Vol. 77, No. 2
February, 1959

American Journal of

OBSTETRICS AND GYNECOLOGY

Gynecology

AN ENDOCRINE BASIS FOR ENDOMETRIAL CARCINOMA*†

ALFRED I. SHERMAN, M.D., AND
RALPH B. WOOLF, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine)

ADENOCARCINOMA of the endometrium has been associated with clinical conditions manifesting widespread metabolic or endocrine imbalance. Well documented is its association with obesity, hypertension, hirsutism, and diabetes. More recently there has been a tendency to associate it also with menstrual disorders and sterility problems during reproductive life. Debatable have been attempts to link carcinoma of the endometrium with hyperestrinism, of either exogenous or endogenous origin. These relationships have been so conspicuous that some authors have generally accepted that there is a type of woman who is prone to develop cancer of the endometrium.

Such generalized endocrinopathies found associated with endometrial cancer have led to the study of the endocrine organs in relationship to this entity. Because of its inaccessibility, the pituitary, though highly suspected, has not been thoroughly studied. The ovary, however, has been subjected to close scrutiny with resultant diverse opinions as to any specific condition associated with endometrial cancer. Particularly debatable have been the conclusions drawn by Woll, Hertig, Smith, and Johnson,[18] of the high incidence of ovarian stromal hyperplasia and diffuse thecomatosis in patients who have adenocarcinoma of the endometrium.

*This work was supported, in part, by an institutional grant from the American Cancer Society to Washington University.

†Presented at the Quadri-City Meeting, St. Louis, Mo., May 17, 1958.

Because of a similar interest in the problem we were led to review carefully all ovaries from patients in whom ovariectomy had been performed as a part of the treatment for endometrial carcinoma. As a control group, all the ovaries of postmenopausal women which were incidentally removed for conditions not related to endometrial carcinoma were scrutinized. The diagnosis of postmenopausal endometrial hyperplasia had been made in some of this latter group.

We had originally intended to correlate and study the stroma for evidence of functional abnormality on a hormonal basis. Unfortunately, we found as did others that the stromal changes were inconsistent. On the other hand, we were so impressed by the large number of hilar cells present in the ovaries of patients who had adenocarcinoma of the endometrium that we reviewed all the ovaries histologically from this point of view. These latter cells have been described since 1922. They have been called by different names, the most common of which are hilar cells, hilus cells, Leydig cells, and sympathicotropic cells. The names are descriptive in that the cells resemble the interstitial cells of the testis and are found in the hilar region of the ovaries. Also, they are often found intimately associated with the sympathetic nerve bundles that are located in the ovarian hilar region. Examination of normal ovaries will disclose the occasional presence of a small group or cluster of these cells.[15] The detection of hilar cells in ovaries of normal individuals will depend greatly upon the care and diligence with which they are sought. For them to be found with any degree of success in normal ovaries usually involves a most careful scrutiny of several sections cut at various levels. That these cells are identical with Leydig cells of the testis is, of course, impossible to prove at the present time. Nevertheless, on an embryological and histological basis they should be similar. The presence of the specific cytoplasmic Reinke crystals further enhances this belief. The hilar cells have a typical appearance and once observed can readily be found on low-power scanning of the tissue sections. They tend to stand out from all other cellular components of the hilum. When detected in ovaries of normal individuals usually only a few isolated cells are present. Seldom, if ever, are they found in large clusters.

The typical hilar cell is polyhedral and the nucleus is basophilic, spheroid, and large. The cytoplasm is acidophilic and abundant in amount. Intracytoplasmic inclusions may be commonly found. These consist of yellow-brown lipochrome pigment granules, sudanophilic droplets, and less frequently Reinke crystalloids. Most often they are located close to the medullohilar border, but they can be seen at times as far as the mesoovarian ligament and on five occasions in our series have been noted within the ovarian stroma close to the hilar border. The cells are usually scattered in groups that seem to line up in planes, or they may be seen in clusters. Association with nerve fibers is common and the cells may at times seem to be contained within them.

The concept of Leydig cells being present in the hilar region of the ovary is acceptable if one is mindful of the embryological development and differentiation of the gonads. In both males and females the genital ridges and mesonephros of the embryo share in the evolution of the adult gonad. Primary sex

cords are elaborated by the germinal epithelium of the genital ridge to blend with simultaneously developing rete cords from the mesonephros. The combined structure of primary sex cords and rete cords composed the medullary component and the celomic germinal epithelium and primordial germ cells compose the cortical component of the undifferentiated primitive gonad. Not until the embryo achieves the 16 mm. stage does the gonad begin to show differentiation according to sex. Whether the primitive gonad will develop into a testis or ovary depends upon the relative development of the medullary and cortical components. In the instance of a testis developing from the primitive gonad, there is a predominance of development of the medullary components. Simultaneously there is regression of the cortical component with no notable secondary sex cord structure being present. In the normal mature testis there is usually no trace of the previous existence of a cortical component in the form of significant vestigial structures. The seminiferous tubules and Leydig cells of the testis are derived from the medullary components. In contrast to the above, the differentiation leading to the development of an ovary is marked by a predominant growth activity of the cortical component. The germinal epithelium gives rise to secondary sex cords and as these progress the medullary components, including the primary sex cords, regress. That the regression of these medullary components is commonly incomplete is apparent from the frequent finding of scattered small nests of rete tubules and Leydig cells in the hilum of otherwise normal ovaries. The prevailing view is that these ovarian hilar Leydig cells like those of the testis function under the control of the anterior pituitary gonadotrophin referred to as the interstitial cell stimulating hormone (ICSH). In females the latter gonadotrophin is termed the luteinizing hormone (LH) and its major role in ovarian physiology is to cause ovulation in a responsive ovary. According to the generally accepted theory of gonadal hormone production the Leydig cells primarily produce androgenic hormones in response to stimulation by the previously mentioned pituitary gonadotrophin LH or ICSH.

Material

This paper is based upon the study of 165 cases of endometrial cancer in which ovariectomy was performed in the course of the surgical phase of treatment. The series has been collected from 1950 to the time of submission of this report. Unfortunately, in 32 of the cases histological sections of the ovaries were inadequate in that the hilar regions were not included in the tissue sections of one or both ovaries. A special effort has been made since the beginning of 1957 to provide adequate ovarian tissue blocks in which a representative portion of the hilum is included. The ovaries removed in 29 cases of endometrial cancer have been subjected to the latter technique. For a control group during the period since 1950 suitable ovarian sections from 86 postmenopausal women were available for study. Included in the latter number have been 52 cases of postmenopausal endometrial hyperplasia. None of the included cases was derived from necropsy sources.

During the early phases of the histological study just described it became apparent that the Leydig cells might be of major significance in the etiology of endometrial carcinoma. Since Leydig cells are hormonally dependent upon the pituitary gonadotrophin, LH or ICSH, we have conducted since the fall of 1957

a corollary study of the urinary excretion of LH in selected patients. The ventral prostate weight technique described by MacArthur and associates,[10] which specifically measures LH, was used to determine the LH excretion in the urine. Assays were performed on 4 hour samples. Six animals were used for each 24 hour collection. In this study there were 31 patients with primary adenocarcinoma of the endometrium whose urine was assayed for the luteinizing hormone. In addition, assays were carried out in 37 patients with a variety of conditions. These included no significant gynecological disease, pre- and postmenopausal endometrial hyperplasia, Stein-Leventhal syndrome, ovarian thecoma, uterine sarcoma, cervical carcinoma, and metastatic adenocarcinoma of the uterus.

There were an additional 20 determinations on 19 patients who had previously been treated for endometrial carcinoma and 4 cases in which pretreatment LH determinations were repeated after administration of Delalutin* (17-hydroxyprogesterone caproate).

Results

The histological portion of this study revealed that there were 133 cases of primary endometrial carcinoma in which ovarian hilar tissue was available for study in at least one section of one ovary. Leydig-cell hyperplasia was present in 109 cases, an incidence of 81.9 per cent. In the 29 cases of primary adenocarcinoma of the uterus studied since the beginning of 1957, the incidence of hilar-cell hyperplasia has been 100 per cent; 29 out of 29 cases.

Study of the control group disclosed that 14 of the 86 cases contained hilar cells, an over-all incidence of 16.3 per cent. Most interesting was the finding that in the 34 controls without evidence of postmenopausal endometrial hyperplasia the incidence of hilar-cell clumps was 2 cases, or 5.88 per cent. In contrast to this, the 52 control patients who presented postmenopausal hyperplasia of the endometrium had an incidence of hilar-cell components of 12 cases, or 23 per cent. Because it is so difficult actually to evaluate the degree of hyperplasia in any histological section, it would be impossible to separate or grade these cases quantitatively. Nevertheless, it is possible to say that as a general rule the number of Leydig cells was much lower in the cases not associated with endometrial cancer. In many the Leydig cells consisted of only 6 to 8 cells in a single clump, and the clumps were usually small and singular, whereas in the tumor patients there were large clumps with numerous cells and usually there were several clumps scattered about. In the cases of endometrial cancer the ovarian hilar regions contained a relative profusion of Leydig cells that were generally distributed in large clusters or as long cords. In some the clusters were large enough to be called adenomas.

In Fig. 1 the results of the assays of urine for luteinizing hormone are depicted. The patients with primary adenocarcinoma of the endometrium had elevated LH levels in 31 out of 31 cases, an incidence of 100 per cent. Following the surgical phase of treatment that included bilateral oophorectomy the level of LH fell to the levels of normal patients in 100 per cent of these cases.

The LH excretion was definitely elevated in 2 postmenopausal women in whom there was definite endogenous steroid stimulation as shown by almost 100 per cent staining of the vaginal smear by iodine vapor. One of these patients had bilateral ovarian thecomas and associated endometrial hyperplasia. The other had secondary papillary adenocarcinoma of the uterus metastatic from the ovary, and, in addition, there was a concomitant granulosa-cell tumor. Finally, one of the 3 patients with premenopausal endometrial hyperplasia studied was found to have a markedly elevated LH excretion (Fig. 1).

*The Delalutin used in this study was supplied by E. R. Squibb & Sons, New York, N. Y.

Posttreatment LH levels were determined in 19 patients in whom no pretreatment LH levels were available. The 12 who were treated by surgery including oophorectomy have LH levels comparable to the levels in normal patients. Three patients treated only by irradiation have elevated levels based on 4 hour urine determinations.

Comment

A review of the literature reveals few reports associating hilar-cell hyperplasia with primary adenocarcinoma of the uterus. Husslein[8] cited 4 cases with this combination of findings. Shaw and Dastur[14] probably were discussing hyperplasia of ovarian hilar Leydig cells in cases of endometrial carcinoma although they did not attempt to establish such an identity. As stated previously, we feel that more reports of a similar nature would be forthcoming if the ovaries obtained from these cases were subjected to more deliberate study.

To arrive at a working hypothesis concerning the nature of the hormonal disorder that eventuates in adenocarcinoma of the endometrium a review of the hormonal physiology of the gonad and pituitary gland is indicated.

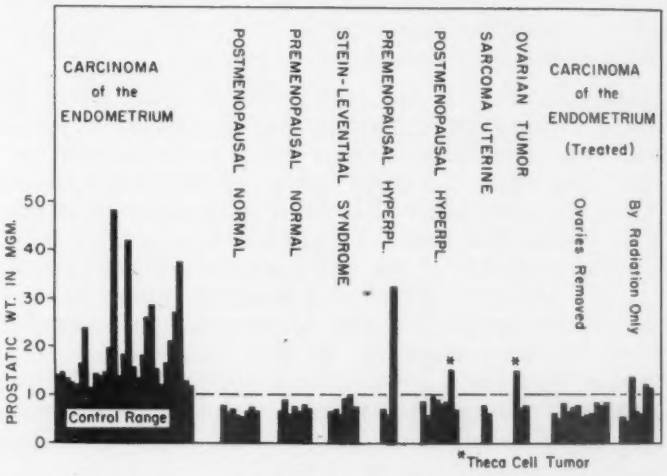


Fig. 1.—This chart presents the relative prostatic weight responses of hypophysectomized rats to a 4 hour aliquot of a 24 hour specimen for various clinical conditions.

The cells of the testis are under the influence of the pituitary gonadotrophins. Sertoli cells under the influence of FSH are presumed to produce estrogens. The growth and hormone production of the Leydig cells is controlled by LH (ICSH) of the hypophysis. Hyperplasia of these cells occurs with the administration of preparations containing LH activity.[6, 11] It must be assumed that these cells also respond when present in the ovary.[16]

As a result of such stimulation the Leydig cells have been shown to produce an androgen.[2] Further proof of such production is the accompanying androgenic effect associated with spontaneous interstitial-cell tumors of the gonad found in man,[13, 15, 17] dog,[7] and mice.[5] In addition, experimentally induced Leydig-cell tumors in mice also share this androgenic effect.[1, 4]

Whether Leydig cells are also capable of producing estrogens is debatable. Certainly the experiments by Maddock and Nelson[11] are convincing. Suspicion is also aroused by the gynecomastia seen accompanying the androgenic effect in patients with spontaneously occurring Leydig-cell tumors. To explain this one must assume the presence of either a single hormone with both estrogenic and androgenic potentialities or two separate hormones. Both explanations are

theoretically possible. Certainly some sex steroids may show a spectrum of biological effects. The recent studies of the biological behavior of synthetic C-19-nortestosterone compounds adds further support to this idea, and, furthermore, some androgenic substances have been shown to be mammotrophic.

Support for the possibility that histologically similar cells may produce other than specific sex hormones may be entertained. Evidence of such situations is seen in the female pseudohermaphrodite. In this condition a congenital enzyme defect causes the adrenal cortical cells to produce biologically abnormal steroid hormones instead of cortisol. It may be that under certain circumstances an acquired metabolic defect of similar nature may play a role in gonadal metabolism. Such reasoning would explain the incongruous situation where a gonadal endocrine tumor comprised of cell types usually associated with one form of clinical picture may in some instances present a diametrically opposite clinical manifestation. Also, to be considered must be the theory of the possibility of admixtures of steroid-producing cells in a tumor to explain the bisexual stimulation. In summary, therefore, it may be stated that Leydig cells might produce one or more hormones and that in either case these may be normally occurring hormones or may perhaps be abnormal hormones. For convenience we should like to refer to this substance as a sexagen. By this we mean any substance which may produce one or more of the basic triumvirate of effects of sex hormones, be it androgenic, estrogenic, or progestational.

Of considerable interest is the fact that estrogens affect the pituitary to produce or release luteinizing hormone. Leydig-cell hyperplasias and tumors can be produced experimentally in mice by the administration of estrogens.[3] This effect of estrogen upon the testis is an indirect one mediated through the release of excessive amounts of pituitary LH with continuous effect on the Leydig cells over a long period of time. To produce such a hormone pattern it must be assumed that the products of the Leydig cells are not capable of playing a feed-back role in the pituitary-gonad axis because, otherwise, the LH would be inhibited. Progesterone is assumed able to suppress LH excretion by the pituitary in the usual feed-back manner. In this connection Fig. 2 is of interest because it indicates that LH excretion is suppressed by 17-alpha-hydroxyprogesterone caproate. We acknowledge that Delalutin is not a natural progestin. As yet, however, unpublished data from our laboratories indicate that it is a progestin in the fullest connotation of the word.

The testis does not produce progesterone although it is well known that androgens such as testosterone and others possess some progestational activity. It may be of interest to assume, therefore, that the Leydig cells under the influence of LH may secrete a sexagen either normal or abnormal which may have one or more of the basic effects of sex hormones. Furthermore, this sexagen may not be capable of playing the feed-back role to the pituitary. Also, to be considered is the possibility that the steroid end products of this proposed biogenesis may well be endowed with biological properties such as carcinogenesis. Certainly, with an abnormal steroid such carcinogenic influence may be considered more likely. It is just as possible that normal steroids in certain combinations and concentrations and under certain hormonal circumstances may have a carcinogenic effect on the endometrial target cells. The latter possibility is enhanced by the work of Meissner and associates.[12] They produced endometrial cancer in normal rabbits and alloxan-diabetic rabbits by multiple intramuscular injections of diethylstilbestrol dipalmitate over a period of many months. Suitable control animals, normal and alloxan diabetic, did not develop the endometrial malignancy. Also, most interesting was the finding by these same authors that the stilbestrol-treated animals which developed adenocarcinoma of the endometrium revealed marked secondary endocrine changes as shown by hypertrophy of ovaries, pituitaries, and adrenal glands.

Germane to this discussion are some clinical observations. The cessation of menses and the onset of the menopause do not mean the cessation of all ovarian function. Actually, evidence of estrogen stimulation in normal women is seen for a decade or more after their last menstrual period. Even in young women estrogen stimulation may be present for years without menses as attested by the cases of hypothalamic amenorrhea. There is evidence that functional relationships between ovary and pituitary as well as ovary and endometrium persist into the postmenopausal state, and there is no reason to doubt the secretion of estrogens from the ovary in the postmenopausal woman.

Also of great interest in the discussion of a hormone etiology for the biogenesis of endometrial cancer are the observations of Jackson and Dockerty.[9] These authors were able to correlate a high incidence of endometrial neoplasms with the Stein-Leventhal syndrome. The abnormal endocrine pattern in these cases is relieved by surgical excision of ovarian tissue. There appears to be a hormone situation in these cases that in some respects resembles the findings in the postmenopausal women who develop endometrial carcinoma. Also, well recognized is the history of abnormal ovarian function and relative sterility during their reproductive years in the patients who develop endometrial carcinoma. Interestingly enough, in some of the cases of Stein-Leventhal syndrome studied by us the LH levels in the urine were elevated, although not as high as in the patients with adenocarcinoma.

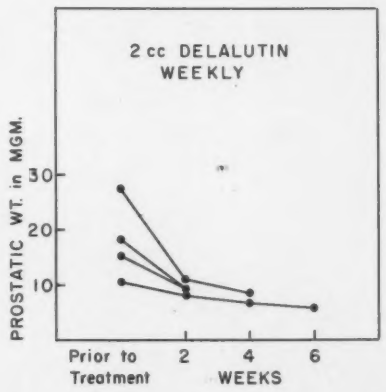


Fig. 2.—This chart demonstrates the drop in urinary LH levels in endometrial cancer patients subsequent to the administration of Delalutin.

According to our concept of the hormonal origin of endometrial cancer we propose that at birth a female destined to develop adenocarcinoma of the endometrium is endowed with an abnormal complement of hilar and/or medullary cells of common embryological origin, whether called Leydig or theca cells. These cells are LH responsive. During the reproductive years of the individual these cells function at a minimum because of the presence of responsive follicular apparatus and its feed-back pituitary control, including the cyclic LH-restraining influence of progesterone from successive corpora lutea. The possibility of subtle deleterious hormone activity from the abnormal hilar and/or medullary cell complement may account for the excessive sterility found in patients with endometrial cancer.

By the advent of the menopause the follicular apparatus has been usually consumed. The restraint of the hormones from the follicular apparatus and subsequent corpora lutea no longer obtain, so that pituitary gonadotrophins are brought to bear fully upon the abnormal hilar and/or medullary cells. The latter produce sexagens that influence the endometrium adversely and cause the

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 3.—Low-power photomicrograph to show clusters of Leydig cells in hilum of ovary.
Fig. 4.—High-power photomicrograph of Leydig cells in hilum of ovary.
Fig. 5.—Low-power photomicrograph to show large group of Leydig cells in hilum of ovary.
Fig. 6.—High-power photomicrograph of typical hilus cells.

pituitary gland to excrete excessive amounts of LH in addition to the usual postmenopausal high FSH levels. We assume that the sexagens are not capable of a feed-back control on the pituitary gland, so that with continued excessive LH activity we find hypertrophy of the hilar and/or medullary-cell component, resulting in Leydig- and/or ovarian stromal-cell hyperplasia. Subsequently, or concomitantly with the latter, the endometrium becomes carcinomatous with independent biogenesis. The hormone situation continues and the excess LH excretion is noted by our results. That the gonads are responsible for the excessive LH excretion is shown in the drop of LH levels following gonadectomy. When radiation therapy alone is used to treat endometrial cancer, the fall of LH excretion is not always noted. Theca and Leydig cells are relatively resistant to radiation, not to mention the relatively small amount of radiation that would reach the gonads in cases treated by intrauterine radium or by x-ray through the thick panniculus of the usual obese patient with endometrial cancer.

Not all patients with postmenopausal endometrial hyperplasia will develop adenocarcinoma of the endometrium. Our LH-excretion studies indicate that in some of these hyperplasia cases there is excessive excretion of this gonadotrophin. Perhaps these patients are destined eventually to develop endometrial malignancy. Obviously, much work remains to be done to carry out further studies on pituitary excretion, and to isolate the sexagen moiety responsible for the eventual development of adenocarcinoma of the endometrium. In addition, corroborative biochemical studies need to be made of the related endocrinopathies found associated with adenocarcinoma of the endometrium.

Furthermore, the theory presented leads to the most provocative thought that by simply introducing into the body a hormone which might act by the proper feed-back action on the pituitary, the endocrine pattern might be interfered with. If this interruption were to occur prior to the time that this neoplasm becomes hormone independent it might inhibit the formation of endometrial cancer. Precedent for such feed-back action on the pituitary is the well-known use of cortisone to inhibit ACTH production in the adrenal hyperplasia syndromes.

From all such possible prophylactic hormones estrogens are deleted. Estrogens have been shown to be capable of increasing LH production and setting up the actual hormonal circumstance shown in this paper to be present in cases of endometrial cancer. Furthermore, in human beings its administration postmenopausally has not seemed to interfere with the development of endometrial carcinoma.

Progesterone, testosterone, and other androgens grouped as progestins, however, may very well be capable of interfering in this cycle. Evidence for this is suggested by the effect of Delalutin in lowering the LH titers shown in Fig. 2. Whether such a drop in LH levels started early enough will inhibit the formation of endometrial carcinoma cannot as yet be shown. The demonstration of such a plausible prophylaxis can come only from a full-scale research program investigating a large group of women.

Fig. 3.—Low-power photomicrograph to show ... in hilum of ovary.
Fig. 4.—High-power photomicrograph of Leydig cells in hilum of ovary.
Fig. 5.—Low-power photomicrograph to show large group of Leydig cells in hilum of ovary.
Fig. 6.—High-power photomicrograph of typical hilar ... cell.

References

1. Bonser, G. M.: J. Path. & Bact. 56: 15, 1944.
2. Brink-Johnsen, T., and Eik-Nes, K.: Endocrinology 61: 676, 1957.
3. Clifton, K. H., Block, E., Upton, A. G., and Furth, J.: Arch. Path. 62: 354, 1956.

4. Gardner, W. U.: Cancer Res. **3**: 92, 1943.
5. Gardner, W. U.: Cancer Res. **3**: 757, 1943.
6. Greep, R. O., Van Dyke, H. B., and Chow, B. F.: Endocrinology **30**: 635, 1942.
7. Huggins, C., and Pazos, R., Jr.: Am. J. Path. **21**: 299, 1945.
8. Husslein, H.: Zentralbl. Gynäk. **73**: 1649, 1951.
9. Jackson, R. L., and Dockerty, M. B.: AM. J. OBST. & GYNEC. **73**: 161, 1957.
10. MacArthur, J. W., Ingersoll, F. M., and Worcester, J.: J. Clin. Endocrinol. **15**: 845, 1955.
11. Maddock, W. W., and Nelson, W. O.: J. Clin. Endocrinol. **12**: 985, 1952.
12. Meissner, W. A., Sommers, S. C., and Sherman, G.: Cancer **10**: 500, 1957.
13. Melicow, M. M., Robinson, J. N., Ivers, W., and Rainsford, L. K.: J. Urol. **62**: 672, 1949.
14. Shaw, W., and Dastur, B.: Brit. M. J. **2**: 113, 1949.
15. Sternberg, W. H.: Am. J. Path. **25**: 493, 1949.
16. Sternberg, W. H., Segaloff, A., and Gaskill, C. J.: J. Clin. Endocrinol. **13**: 139, 1953.
17. Warren, S., and Olshausen, K. W.: Am. J. Path. **19**: 307, 1943.
18. Woll, E., Hertig, A. T., Smith, G. V., and Johnson, L. C.: AM. J. OBST. & GYNEC. **56**: 617, 1948.

THE ASSOCIATION OF DIABETES MELLITUS AND CARCINOMA OF THE ENDOMETRIUM

JOHN B. VANDER, M.D.,* PONDVILLE, MASS.

(From the Pondville Hospital {Massachusetts Department of Public Health}, Walpole, Mass., and the National Cancer Institute, United States Public Health Service)

DIABETES mellitus has been reported frequently as occurring more often among patients with carcinoma of the endometrium than can be accounted for by chance alone. The implication is that there is a definite relationship between these two diseases. Publications which best support this hypothesis are those of Scheffey,[1] Palmer,[2] and Way,[3] whose figures are summarized in Table I.

TABLE I. PERCENTAGE OF PATIENTS WITH CARCINOMA OF THE ENDOMETRIUM WHO ALSO HAD DIABETES MELLITUS

AUTHOR	YEAR	NO. OF PATIENTS WITH ENDOMETRIAL CANCER	% WITH DIABETES
Scheffey	1943	127	11.0
Palmer	1949	165	16.9
Way	1954	106	29.0

These figures indicate that the number of patients with true diabetes among those with carcinoma of the fundus uteri is between two and five times that in the general population. They provide a basis for speculations, such as those of Way, that a common etiological factor may be present, possibly related to pituitary function. Other reports, however, including those of Marble,[4] Smith,[5] and Jacobson,[6] have failed to confirm these findings.

The concept of a common etiological agent is an attractive one. Further test of the validity of the data upon which it is based seems necessary, however, in view of the conflicting evidence which now prevails. In order to provide additional data, all figures of the Pondville Hospital from the time of its beginning in 1929 until the end of 1957 were examined. The number of patients with carcinoma of the endometrium who also had diabetes was determined and a comparison made with the number of expected cases based on comparable age groups in the general population with the use of the prevalence rates established by Wilkerson[7] in the Oxford Study of 1947. These rates are shown in Table II.

The observed and expected percentages of diabetic patients among those with endometrial carcinoma at the Pondville Hospital are shown in Table III.

It is evident from a comparison of the observed percentage of 5.6 diabetics among the patients with carcinoma of the endometrium in this series with the expected percentage of 5.4, based on the Oxford prevalence rates, that there is no significant difference between them.

*Staff, National Cancer Institute.

TABLE II. PREVALENCE OF DIABETES IN A SAMPLE FEMALE POPULATION (FIGURES AFTER WILKERSON, OXFORD STUDY, 1947)

AGE INTERVAL	TOTAL FEMALE POPULATION	% WITH DIABETES
All ages	2,468	1.8
Under 15	619	0.0
15-24	372	0.3
25-34	417	0.2
35-44	342	1.3
45-54	275	4.0
55-64	196	6.9
65-74	162	5.2
75 and over	85	6.7

TABLE III. OBSERVED AND EXPECTED PERCENTAGES OF DIABETIC PATIENTS AMONG THE 483 WITH CARCINOMA OF THE ENDOMETRIUM

AGE INTERVAL	TOTAL CASES OF CARCINOMA OF ENDOMETRIUM	OBSERVED % DIABETES	EXPECTED DIABETES ACCORDING TO PREVALENCE RATES OF OXFORD STUDY	
			%	NO.
All ages	483	5.6	5.4	26.3
15-24	0	0.0	0.3	0.0
25-34	4	0.0	0.2	0.0
35-44	28	0.0	1.3	0.4
45-54	90	3.3	4.0	3.6
55-64	162	6.1	6.9	11.2
65-74	148	6.8	5.2	7.7
75 and over	51	7.9	6.7	3.4

Comment

The wide variation in percentages of diabetic patients found among those with carcinoma of the endometrium seems best explained by differences in criteria used in establishing the diagnosis of the diabetes mellitus. At the Pondville Hospital, diagnoses were based on clinical history and laboratory evidence of glycosuria and elevated fasting blood sugars. Routine glucose tolerance tests were not done, however. All diagnoses represented patients with clinical diabetes who required treatment either by dietary restriction or with insulin. That a significant number of cases of true diabetes remained undiagnosed during the course of the patients' hospitalization for endometrial carcinoma seems unlikely in view of the continued interest of the Pondville staff in the alleged association of these two diseases which has extended over a period of many years.

The criteria used by Scheffey are not given. Palmer's diagnoses rest upon fasting blood sugar determinations greater than 120 mg. per cent and also glucose tolerance tests, the exact technique of which is not described. Way, who reports 29 per cent of diabetics, performed glucose tolerance tests on all 106 patients, using a 2-hour blood sugar level of 300 mg. per cent as a diagnostic requirement. In no paper, however, is mention made of the state of nutrition, the type of previous diet, or the status of liver function, all of these being factors well known to affect glucose tolerance curves significantly.

Thus there is the possibility that many patients with the diagnosis of true diabetes had abnormal glucose tolerance tests only. A paper by Moss,[8]

who performed glucose tolerance studies on 23 consecutive patients with endometrial carcinoma and reported 75 per cent as having diabetes mellitus, is especially suggestive of this. A pertinent discussion of the significance of abnormal glucose tolerance curves in patients with malignant disease is contained in a paper by Glicksman and co-workers.[9] They call attention to the high incidence of hyperglycemic responses to glucose tolerance tests in all types of malignancy, but make a sharp distinction between hyperglycemia and true diabetes.

In conclusion, it seems difficult to accept as valid, at the present time, the hypothesis of a positive association between diabetes mellitus and carcinoma of the endometrium. The inclusion of patients who have abnormal glucose tolerance tests only with those who have true diabetes seems a possible explanation for the high percentages of diabetic patients reported by others.

Summary

In a study of 483 consecutive patients with carcinoma of the endometrium, 5.6 per cent were found to have diabetes mellitus as compared with 5.4 per cent in the general population of the same sex and age.

These figures do not confirm the hypothesis that there is a positive association between diabetes mellitus and endometrial carcinoma.

Appreciation is expressed to Dr. Joe Vincent Meigs who helped in the preparation of this paper and supervised the surgical care of many of the patients used in this study.

References

1. Scheffey, L. C., Thudium, W. J., and Farell, D. M.: Am. J. Obst. & Gynec. **46**: 786, 1943.
2. Palmer, J. P., Reinhard, M. C., Sadugor, M. G., and Goltz, H. L.: Am. J. Obst. & Gynec. **58**: 457, 1949.
3. Way, S.: J. Obst. & Gynaec. Brit. Emp. **61**: 46, 1954.
4. Marble, A.: New England J. Med. **211**: 339, 1934.
5. Smith, G. V.: New England J. Med. **225**: 608, 1941.
6. Jacobson, P. H.: Milbank Mem. Fund Quart. **26**: 90, 1948.
7. Wilkerson, H. L. C., and Krall, L. P.: J. A. M. A. **135**: 209, 1947.
8. Moss, W. T.: Am. J. Roentgenol. **58**: 203, 1947.
9. Glicksman, A. S., Myers, W. P. L., and Rawson, R. W.: M. Clin. North America **40**: 887, 1956.

MESENCHYMAL SARCOMAS OF THE UTERUS

WILLIAM B. OBER, M.D., AND HAROLD M. M. TOVELL, M.D.,
NEW YORK, N. Y.

(From the Department of Surgical Pathology, College of Physicians and Surgeons, Columbia University and the Sloane Hospital for Women, and Francis Delafield Hospital, Columbia-Presbyterian Medical Center; and the Department of Pathology, Knickerbocker Hospital)

SARCOMA of the uterus represents 3 per cent or less of all malignant neoplasms of that organ. In a recent communication, one of us[1] proposed a classification of uterine sarcomas in four major groups: (1) leiomyosarcoma, (2) mesenchymal sarcoma, (3) blood vessel sarcoma, and (4) lymphoma. Of these, leiomyosarcoma is the most frequent, constituting 50 to 75 per cent of all uterine sarcomas. Novak and Anderson[2] classified 39 (66.1 per cent) of their 59 uterine sarcomas as leiomyosarcoma. MacFarlane's[3] study of 42 uterine sarcomas included 31 cases of leiomyosarcoma (73.8 per cent), 4 cases of endometrial stromal sarcoma, 3 cases of carcinosarcoma, and 4 other cases of less frequently encountered histologic types. More recently Webb[4] reported 42 cases of uterine sarcoma, including 22 cases of leiomyosarcoma (52 per cent) and 20 cases of mesenchymal sarcoma (48 per cent).

The present communication deals with 29 examples of uterine sarcoma, of which 28 occurred in adults and one in an infant; 26 of these cases are in the group of mesenchymal sarcoma. We have deliberately excluded all cases of leiomyosarcoma whether arising in a leiomyoma or arising diffusely in the uterine wall. The anatomic diagnoses are listed in Table I.

TABLE I. ANATOMIC DIAGNOSES IN 29 CASES OF UTERINE SARCOMA

Mesenchymal sarcoma		26
A. Pure, homologous:		
Endometrial stromal sarcoma	4	
Stromatous endometriosis (endolymphatic stromal myosis)	1	
B. Pure, heterologous:		
Rhabdomyosarcoma	1	
C. Mixed, homologous:		
Carcinosarcoma	8	
D. Mixed, heterologous:		
Carcinosarcoma	8	
Mixed mesenchymal sarcoma	3	
Sarcoma botryoides vaginae puellae	1	
Blood-vessel sarcoma		1
A. Hemangiosarcoma (hemangioendothelioma)*	1	
Lymphoma†		2
A. Reticulum-cell sarcoma	1	
A. Lymphosarcoma	1	

*Previously reported in detail by Stout.[23]
†To be reported in detail subsequently.

In selecting these cases, care was taken to exclude examples in which the often-repeated claim could be made that the sarcoma was in reality a poorly differentiated carcinoma masquerading as a nonepithelial tumor. Likewise, cases in which the pathologic material was insufficient for accurate classification were also omitted. Twenty-five of the cases are from the files of hospitals within the Columbia-Presbyterian Medical Center; the remaining 4 cases are from the consultation files of the senior author.*

The nomenclature within this family of tumors is as rich and varied as their histology. McFarland[5] listed 119 different terms which have been applied to these tumors, some based upon gross appearance, others upon predominance of one or more cell types of histologic patterns, and still others upon a variety of attributes, often including a mixture of Greek and Latin roots. In recent years, the term leiomyosarcoma has become well standardized. The terms "mixed mesodermal tumor," "mixed mesenchymal Müllerian sarcoma," and "combined mesenchymal sarcoma and carcinoma" have been used for the mesenchymal sarcomas of mixed varieties, and cell-specific terms such as rhabdomyosarcoma and chondrosarcoma have been applied to the pure varieties. No one perfectly satisfactory term has been devised for this group. Our own general term "mesenchymal sarcoma" is incomplete, for it appears to exclude the examples in which admixed neoplastic epithelial elements are prominent. The only defense against this charge is that the presence of the neoplastic *mesenchymal* elements makes this tumor distinctive and distinguishable from the garden varieties of uterine adenocarcinoma.

Embryogenetic Considerations

The Müllerian duct arises as an invagination of the posterolateral wall of the celom in the urogenital ridge. The epithelial cells of the duct are the direct descendants of celomic lining cells. Before the celomic lining cells assume their typical epithelial character, they appear as intermediate forms between epithelium and mesenchyme. According to Gruenwald's[6, 7] studies on 20-25 mm. (6-8 week) human embryos there is every indication that an exchange of cells takes place between the celomic lining cells and the underlying mesenchymal cells. In subsequent embryonic development of organs such as the adrenal cortex and the gonads, this close relationship between epithelium and mesenchyme becomes more apparent.

As the Müllerian duct grows caudally in the form of an epithelial column surrounded by a zone of concentrically dispersed mesenchymal cells, transitions from epithelium into the surrounding mesenchyme occur. So intimate is the relationship between epithelium and mesenchyme in this stage that the term "Müllerian apparatus" has been suggested to include both elements. It is from this apparatus that the fused uterus and unfused uterine tubes normally develop. The caudal tip of the growing Müllerian duct is enclosed by a common basement membrane with the more medially situated Wolffian duct. As the two ducts grow caudally, the more mature portion of the Müllerian

*Sixteen cases are from the Sloane Hospital for Women, 8 cases from the Francis Delafield Hospital, and one case from Babies' Hospital.

duct becomes pinched off and lies within its own basement membrane surrounded by mesenchyme derived from the epithelial cells of the duct. Likewise, the tubal ridge, the thickened area of the celomic wall overlying the Müllerian duct, transforms its basal portion into mesenchyme which further contributes to the Müllerian duct. Thus, as Gruenwald points out, the mesenchymal portions of the uterus and tubes are derived from the Müllerian duct epithelium and the celomic epithelium overlying the duct.

Although the close relationship of epithelium and mesenchyme does not normally manifest itself in the fully developed uterus by transitional cell form, it may well be reflected in the potentialities of these cells, as suggested by such pathologic phenomena as carcinosarcoma of the uterus.

Earlier, Pfannenstiel[8] had enunciated the theory that the variety of cellular elements in mixed tumors represented metaplasia of a pluripotent tissue. Midway between the schools of displaced tissues and metaplasia was the position of Schwalbe,[9] who developed the concept of a "dysontogenetic field." This implied an error in cell development determined early in embryonic life, not necessarily in the form of a visibly different cell or group of cells, but in the form of a potentiality to undergo neoplasia when appropriate conditions obtained. Later, Albrecht[10] stated that tumor formation was essentially like organ formation and that tumors did not arise on the basis of primary cellular errors but rather as embryonic or postembryonic errors in organ development. In large measure, Nicholson[11] subscribed to this theory, citing evidence that tumor growth is not completely lawless, but rather conforms in part to the general laws which govern the growth and differentiation of nonneoplastic cells and tissues. Intermingled with this was considerable stress upon anomalies, either of bulk, blending, position, or differentiation, as being the basis of tumor growth. The specific cellular changes, according to Nicholson, were described as "dedifferentiation and rejuvenescence."

In more recent years, Willis[12] has denounced theories involving "rests" most vigorously, stating that it is most improbable that a cell rest should lie dormant in the endometrium during 30 to 40 years of cyclical sloughing, only to give rise to a tumor after the menses cease. Currently, most observers feel that in the adult variety of this family of tumors, the site of origin is the differentiated endometrial stromal cell. Endometrial stroma, though fully differentiated, is the least highly specialized cell type derived from Müllerian mesenchyme. It is plausible that under conditions of neoplasia it can so modify its nature as to give rise to any or all of the possible derivatives of immature mesenchyme, either singly or in concert.

Tissue much like the endometrial stroma can be found in a variety of locations in the female pelvis, notably the endocervix, the endosalpinx, and directly beneath the peritoneal coatings of the uterus, tubes, ovaries, bladder, omentum, sigmoid, and vermiform appendix, as well as beneath the capsule of pelvic lymph nodes. This is evidenced by the congruent distributions of the ectopic decidual reaction and of pelvic endometriosis. Occasional examples of tumors of similar histologic structure have been reported in these locations.

A similar histogenesis is ascribed to sarcoma botryoides, the juvenile member of this family. However, its distinctive gross appearance as well as its characteristic age distribution makes it reasonable to consider that its pathogenesis may be different. The fact that an occasional case of botryoid sarcoma has been reported to be present at birth certainly implies that the basis for its development was determined in embryonic life and the mechanism for its continued growth and development were also present in embryo. The extent to which postnatal influences affect the appearance of botryoid sarcomas that appear several years after birth cannot be assessed.

In our opinion, the mesenchymal sarcomas of the uterus constitute a family of tumors which share a common histogenesis, being derived from tissues which develop from the mesenchyme formed from and surrounding the Müllerian duct in the urogenital ridge. Carcinosarcoma includes in addition epithelial elements, usually glandular, occasionally squamous, which are derived from Müllerian epithelium proper. Common histogenesis need not imply common pathogenesis; there is good reason to believe that because of the distribution of these tumors in terms of age and location in the genital tract they can arise under a variety of circumstances.

Taxonomy

The detailed classification of uterine sarcomas has been presented in a previous communication.[1] The only portion which merits recapitulation is that dealing with mesenchymal sarcomas. These are subdivided in terms of the categories of Zenker[13] who classified them as *pure* (i.e., composed of one cell type only) and *mixed* (i.e., composed of more than one cell type), and as to whether they were *homologous* (i.e., contained tissue elements entirely indigenous to the uterus) or *heterologous* (i.e., contained tissue elements foreign to the uterus, e.g., cartilage, striated muscle, etc). The anatomic diagnoses in Table I are arranged in terms of this scheme. It is evident that a carcinosarcoma is perforce a mixed tumor, but its stroma may contain heterologous elements or it may be composed entirely of elements more closely related to the endometrial stroma from which it arose. Likewise, the idea of a pure heterologous sarcoma such as a rhabdomyosarcoma or a chondrosarcoma of the uterus represents a quantitative distinction. The heterologous mixed mesenchymal sarcomas contain a greater proportion of undifferentiated mesenchymal sarcoma whereas the "pure" variety is almost entirely composed of neoplastic mesenchymal cells which have specialzed along one particular route. Indubitably, admixed with the extensive areas of chondrosarcoma and rhabdomyosarcoma are scattered neoplastic cells which have not differentiated at all.

The common denominator in all these tumors is the mesenchymal sarcoma component. Alznauer[14] labeled it "undifferentiated cellular sarcoma"; Sternberg, Clark, and Smith[15] labeled some of it "endometrial sarcoma," presumably the areas that resemble the pure homologous variety, and some "unclassified sarcoma," presumably the areas in which there is a proliferation of neoplastic cells without characterizing morphologic features. Symmonds and Dockerty[16]

TABLE II. SUMMARY OF DATA ON PURE HOMOLO

PATIENT	NO.	FIGS.	AGE	AGE AT MENOPAUSE	SYMPTOMS	EXAMINATION
Endometrial Stromal Sarcoma, 4 Cases.—						
F. W.	SH 527955		47	Not known	Not obtainable	Uterus enlarged 3 times. Broad ligaments infiltrated
T. Z.	SH 974334	4 and 5	39	–	Menorrhagia 5 months	Uterus enlarged twice. Pedunculated 3 cm. polyp protruding through cervical os. Hgb. 10 Gm.
M. J.	SH 080210	1, 2, and 3	55	51	Episodic staining	Uterus slightly enlarged. Mass in cervix, 10 by 6 cm.
M. T.	SH 102712	6, 7, and 8	55	51	Continuous bleeding 2 months	Uterus slightly enlarged
Stromatous Endometriosis, 1 Case.—						
L. C.*	SH 260707	9, 10, and 11	32	–	Menorrhagia 6 months	Uterus enlarged 3 times

*Reported by Corscaden.[19]

TABLE III. SUMMARY OF DATA ON PURE HETERO

PATIENT	NO.	AGE	AGE AT MENOPAUSE	SYMPTOMS	EXAMINATION
Rhabdomyosarcoma, 1 Case.—					
L. L.	FDH 9885	65	50	Abdominal pain, weight loss, 3 months	Uterus enlarged 3 times. Hematometra. Hgb. 8.8 Gm.

TABLE IV. SUMMARY OF DATA ON MIXED HOMOLO

PATIENT	NO.	FIGS.	AGE	AGE AT MENOPAUSE	SYMPTOMS	EXAMINATION
Carcinosarcoma, 8 Cases.—						
F. M.	SH 049362		58	55	Episodic staining, 2 years	Uterus slightly enlarged
C. M.	SH 968658		63	51	Episodic bleeding, 1 month	Uterus enlarged 3 times
A. S.*	SH 605467	13, 14, and 15	63	48	Slight episode of staining, 1 week	Uterus enlarged twice
B. J.	FDH 4394		63	48	Daily staining, 3 months	Uterus enlarged twice
L. S.	FDH 6276		54	50	Bleeding, 4 months	Uterus enlarged twice
G. K.	FDH 5091	16-21	65	55	Episodic staining, 1 year	Frozen pelvis. Polypoid mass in cervix. Hgb. 11 Gm.
P. S.	CS 5037		61	49	Bleeding, 2 months	Uterus enlarged twice. Mass in cervix
M. G.	FDH 5191		57	43	Staining, 1 month	Uterus slightly enlarged

*Reported by Watson.[20]

HOMOLOGOUS UTERINE SARCOMAS

TREATMENT	FOLLOW-UP	METASTASES
Supravaginal hysterectomy, right salpingo-oophorectomy. Tumor transected at operation. Complete pelvic x-ray cycle	Died of disease 11 years	Lung (x-ray); generalized (clinical)
D&C., total abdominal hysterectomy, bilateral salpingo-oophorectomy	Lost to follow-up	----------
D&C., total abdominal hysterectomy, bilateral salpingo-oophorectomy. Intravaginal radium 1 year postoperatively	Alive and well 5 years. Died of intercurrent disease 8 years (breast ca.)	Suburethral mass 1 year (no biopsy)
Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Alive and well 5 years	----------
D&C., supravaginal hysterectomy. X-ray to pelvis 4 years postoperatively	Died of intercurrent disease 15 years (myelogenous leukemia)	Abdominal scar, 3 years (excised—same as primary). Pelvic mass, 4 years, obstructing ureter (regressed following x-ray)

HETEROLOGOUS UTERINE SARCOMAS

TREATMENT	FOLLOW-UP	METASTASES
D&C, total abdominal hysterectomy, bilateral salpingo-oophorectomy	Alive with disease 9 months	Lungs (x-ray), at time of operation

HOMOLOGOUS UTERINE SARCOMAS

TREATMENT	FOLLOW-UP	METASTASES
D&C. Radium 5,200 mg. hr.	Died of disease 1 year	Vagina and suburethral area, 2 months (no biopsy)
D&C, total abdominal hysterectomy, bilateral salpingo-oophorectomy. Complete pelvic x-ray cycle	Died of disease 18 months	Vagina, 1 year (biopsy): undifferentiated adenocarcinoma). Generalized abdominal metastases (clinical)
Total abdominal hysterectomy, right salpingo-oophorectomy. X-ray to pelvis 6 months postoperatively	Died of disease 1 year	Ovary at operation: adenocarcinoma. Vagina at 6 months: stromal sarcoma. Generalized abdominal metastases (clinical)
D&C. Operated upon elsewhere	Alive and well 3 years	----------
Total abdominal hysterectomy, right salpingo-oophorectomy. Complete pelvic x-ray cycle	Alive and well 1 year	----------
Inoperable. Cobalt therapy to pelvis and abdomen (5,600 r total tumor dose)	Died of disease 6 months	Autopsy: adenocarcinoma metastatic to lungs, liver, and aortic lymph nodes. Died of uremia with large abdominopelvic mass
Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Alive and well 7 years	----------
Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Cobalt, 5,000 r total tumor dose 6 months postoperatively	Died of disease 1 year	Autopsy: adenocarcinoma metastatic to omentum, peritoneum, aortic lymph nodes. Squamous carcinoma in one irradiated node

called it "fibromyxosarcoma," apparently when well differentiated, and "endometrial stromal sarcoma" when less well differentiated. Irrespective of the choice of words, it remains the essential part of the tumor; everything else is either derived from it or added to it.

TABLE V. SUMMARY OF DATA ON MIXED

PATIENT	NO.	FIGS.	AGE	AGE AT MENOPAUSE	SYMPTOMS	EXAMINATION
Carcinosarcoma, 8 Cases.—						
D. W.	SH 289574		50	45	Bleeding 2 weeks	Uterus enlarged 3 times. Polypoid mass in cervix
A. W.	SH 743890		56	52	Staining 4 years Bleeding 2 months	Uterus enlarged 4 times. Polypoid mass in cervix
E. F.	SH 029072		68	45	Daily bleeding 8 months	Uterus enlarged 6 times. Polypoid mass in cervix. Hgb. 10 Gm.
J. B.	FDH 4379	22	74	50	Bleeding 3 months. Enlarging abdominal mass 2 years	Uterus enlarged 5 times. Class V Papanicolaou smear
I. T.	SH 854449	23 and 24	63	52	Bleeding 8 months	Uterus enlarged 6 times. Polypoid mass in cervix. Hgb. 6.5 Gm.
J. G.	FDH 3409	25	65	55	Crampy pelvic pain 1 week	Uterus enlarged 3 times. Introital mass. Frozen pelvis. Hgb. 11 Gm.
C. J.	FDH 5529	26-32	74	50	Bleeding 2 months	Uterus slightly enlarged. Polypoid mass in cervix
E. B.	SH 209817		51	40 (X-ray)	Staining 17 days	Uterus normal in size
Mixed Mesenchymal Sarcoma, 3 Cases.—						
M. S.*	SH 910046		58	50	Bleeding 3 months	Uterus enlarged 3 times
G. J.	SH 103440		56	44	Bleeding 4 months. Abdominal swelling	Uterus enlarged 3 times. Polypoid mass in cervix. Hgb. 9.2 Gm.
F. P.	FDH 3204	33	60	Not known	Abdominal mass. Pelvic pain 3 months	Uterus enlarged 3 times
Sarcoma Botryoides Vaginae Puellae, 1 Case.—						
F. W.*	BH 266364	34 and 35	15 months	-	Introital mass 4 days	Polypoid mass in introitus

*Reported by Corscaden.[19]

Symmonds and Dockerty applied the term carcinosarcoma to the mixed homologous variety and "mesodermal mixed tumor" to the mixed heterologous variety. This is purely a divergence in vocabulary and does not reflect any disagreement as to the nature, composition, or behavior of the tumors.

HETEROLOGOUS UTERINE SARCOMAS

HETEROLOGOUS TISSUE	TREATMENT	FOLLOW-UP	METASTASES
Rhabdomyosarcoma	D&C. Radium (7,000 mg. hr.). Laparotomy. Biopsy at 9 months	Died of disease 9 months	Autopsy: adenocarcinoma metastatic to liver, peritoneum, omentum, and retroperitoneal lymph nodes
Rhabdomyosarcoma	D&C. Complete pelvic x-ray cycle	Died of intercurrent disease 5 weeks. ? embolus	Ascites (terminal). Abdominal metastases (clinical)
Chondrosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Complete pelvic x-ray cycle	Died of disease 8 months	Adenocarcinoma in tubes and ovaries at operation. Metastases to mediastinum and retroperitoneum by x-ray. Metastatic adenocarcinoma in femur—biopsied
Chondrosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Cobalt therapy (6,000 r total tumor dose)	Died of disease 7 months	Papillary adenocarcinoma in ovaries and mesovarium at operation, metastatic to supraclavicular node at 6 months
Rhabdomyosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Complete pelvic x-ray cycle	Died of disease 11 months	Local abdominopelvic recurrence—no biopsy. Obstructed ureter
Rhabdomyosarcoma	D&C. Laparotomy, biopsy of omentum. Inoperable	Died of disease 4 months	Tumor cells in ascites. Carcinosarcoma in omentum (biopsy). Palpable metastases in liver. Metastases to lung (x-ray)
Rhabdomyosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Left pelvic lymphadenectomy. Palliative x-ray to neck and pelvis 1 year	Died of disease 18 months	Adenocarcinoma metastatic to lungs, adrenals, and lymph nodes. Squamous carcinoma in irradiated pelvic mass. Undifferentiated carcinoma in supraclavicular lymph node
Chondrosarcoma	D&C. Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Alive and well 18 months	----------
Chondrosarcoma	D&C. Total abdominal hysterectomy, bilateral salpingo-oophorectomy. Complete pelvic x-ray cycle	Alive and well 10 years	----------
Rhabdomyosarcoma	Total abdominal hysterectomy, bilateral salpingo-oophorectomy for papillary serous cystadenocarcinoma of ovary	Died 10 days postoperatively (peritonitis)	Autopsy: ovarian carcinoma in liver, omentum, diaphragm, and retroperitoneal lymph nodes
Leiomyosarcoma. Rhabdomyosarcoma	Supravaginal hysterectomy, left salpingo-oophorectomy. Palliative x-ray to pelvis	Died of disease 1 month	Autopsy: residual sarcoma in pelvis with extension to retroperitoneum and metastases to peritoneum
Rhabdomyoblasts (scattered)	Total pelvic exenteration	Alive with disease 9 months	Massive pelvic recurrence (biopsied) 5 months

Robert Meyer[17] pointed out that mixed sarcomas of the uterus might be classified as (1) collision tumors, in which there is accidental collision of two originally descrete or separate tumors, (2) combination tumors, in which the single essential parts have a common histogenesis . . . a union with various possibilities, and (3) composition tumors, mixed tumors in which both stroma and parenchyma are blastomatous without being histogenetically related. One of the cases of carcinosarcoma in this series is a collision tumor; the remaining 15 are all combination tumors. Composition tumors cannot arise in the endometrium for both glands and stroma are histogenetically related.

Clinical Features

The essential clinical features of the 26 cases of mesenchymal sarcoma in this series are tabulated according to our classification in Tables II to V.

Incidence.—The 22 cases of mesenchymal sarcoma from the Columbia-Presbyterian Medical Center reported in this series were seen during the same period in which Corscaden and Singh[18] collected 32 cases of leiomyosarcoma. It appears that the mesenchymal sarcomas occur less frequently than the leiomyosarcomas.

Age, Parity, and Ethnic Origin.—All but 3 of the patients with mesenchymal sarcomas were postmenopausal and, excluding the 15-month-old infant with sarcoma botryoides, had an average age of 58.9 years. This is slightly above the average age of 52-58 years reported by various authors for endometrial adenocarcinoma. The average age at the time of the menopause in these patients was 49.9 years.

The average age of the 4 patients with endometrial stromal sarcoma and the one patient with stromal endometriosis was 45.6 years, while that of the patients with carcinosarcoma was 62.4 years.

Twelve, or 48 per cent, of the patients had not borne children. Of the 29 patients, 7 were Negroes and 22 were white, including 6 Jewish women, 2 Puerto Ricans, and 1 Egyptian.

Symptoms.—No symptoms distinguished mesenchymal sarcoma of the uterus from other neoplasms of this organ. Of the 26 patients, all but 3 complained of varying degrees of vaginal bleeding. Two patients complained primarily of crampy abdominopelvic pain, one of whom had a hematometra and one a large necrotic mass protruding through a dilated cervix and introitus. The degree of bleeding varied from episodic to continuous "staining"

Fig. 1.—Endometrial stromal sarcoma. A nonneoplastic gland is surrounded by neoplastic endometrial stroma showing cellular pleomorphism and hyperchromasia. (×200; reduced ⅓.)

Fig. 2.—Endometrial stromal sarcoma. Poorly fasciculated bipolar cells are admixed with scattered "round" cells. (×100; reduced ⅓.)

Fig. 3.—Endometrial stromal sarcoma. An ill-defined nest of "round cells" resembling adult endometrial stroma is surrounded by pleomorphic and hyperchromatic cells. (×100; reduced ⅓.)

Fig. 4.—Endometrial stromal sarcoma arising in a polyp. Low-power view showing cystically dilated glands with a cellular intervening stroma. (×35; reduced ⅓.)

Fig. 5.—Endometrial stromal sarcoma arising in a polyp. Detail of Fig. 4 showing pleomorphism, hyperchromasia, and disturbed pattern of the stromal complement. (×100; reduced ⅓.)

Fig. 6.—Endometrial stromal sarcoma with transition to stromatous endometriosis. Low-power view showing cellular stromal sarcoma toward the endometrial cavity and endolymphatic pattern at the invading edge. (×5; reduced ⅓.)

Fig. 7.—Endometrial stromal sarcoma showing transition to stromatous endometriosis. Detail showing an aggregate of closely packed uniform stromal cells lying within a preformed endothelium-lined channel. (×40; reduced ⅓.)

Fig. 8.—Endometrial stromal sarcoma with transition to stromatous endometriosis. Detail of the stromal sarcoma near the endometrial surface showing pleomorphic stromal cells growing without definable pattern. (×100; reduced ⅓.)

Fig. 1.

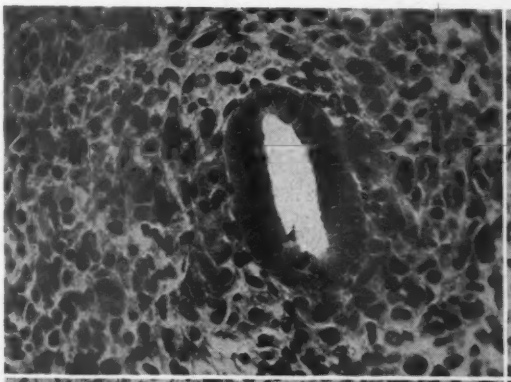


Fig. 2.

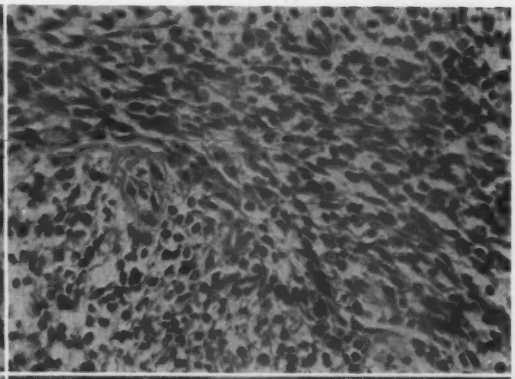


Fig. 3.

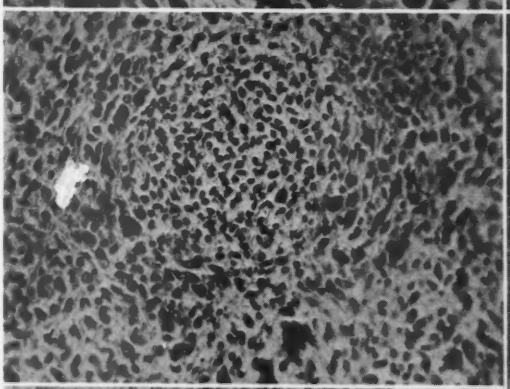


Fig. 4.

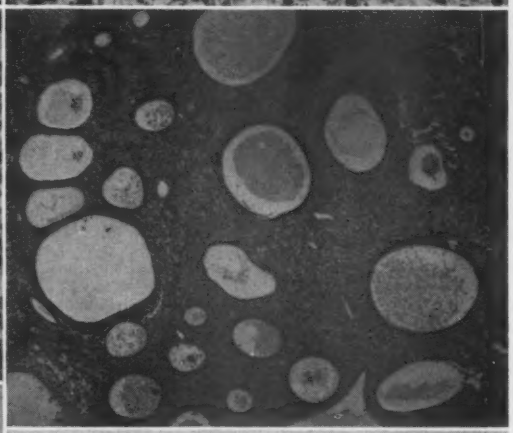


Fig. 5.

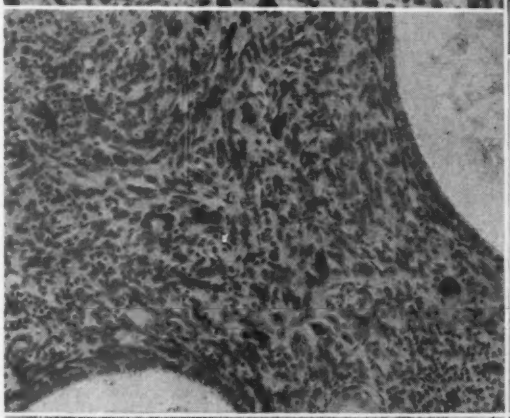


Fig. 6.

Fig. 7.

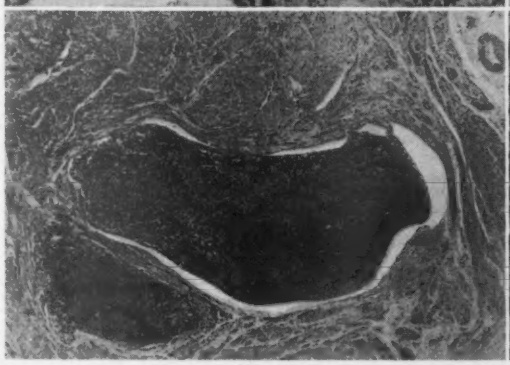
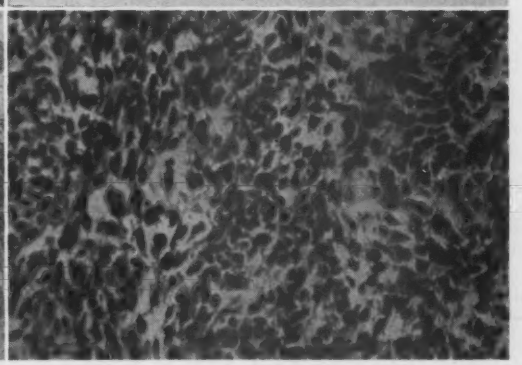


Fig. 8.



Figs. 1-8.—*For legends see opposite page.*

to "heavy bleeding." Two patients, one with endometrial stromal sarcoma and one with stromatous endometriosis, were premenopausal, and both complained of menorrhagia of 5 and 6 months' duration, respectively. Only one patient in this series had received previous pelvic irradiation for menorrhagia.

Examination.—Five patients were severely anemic as a result of blood loss. An enlarged uterus, varying from "slightly enlarged" to the size of

Fig. 9.

Fig. 10.

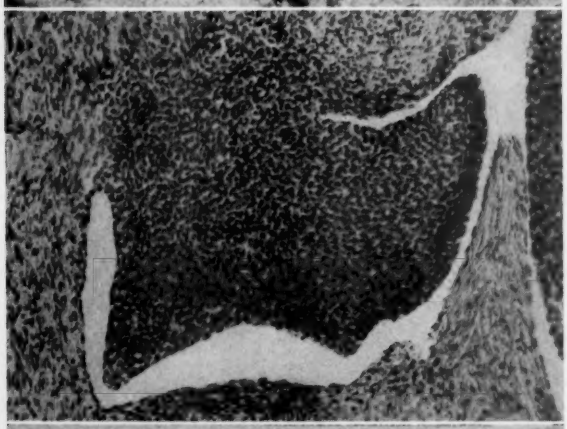


Fig. 11.

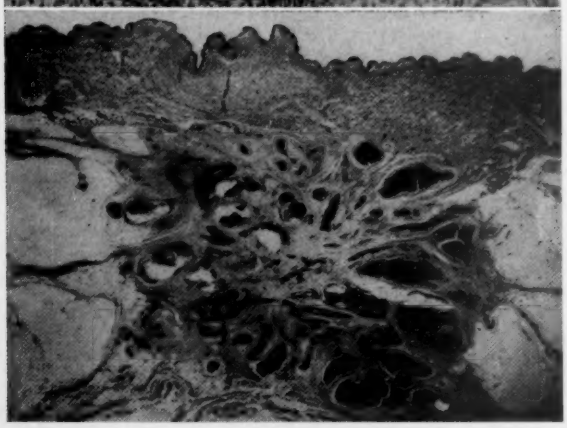


Fig. 9.—Stromatous endometriosis. Low-power view showing aggregates of stromal cells within the myometrium, some of which are in preformed spaces. (×20; reduced ¼.)

Fig. 10.—Stromatous endometriosis. Detail of Fig. 9 showing a mass of uniform cells growing into an endothelium-lined channel. (×100; reduced ¼.)

Fig. 11.—Stromatous endometriosis. Low-power view showing recurrence in abdominal scar with preservation of the endolymphatic pattern. (×20; reduced ¼.)

a 6 months' pregnancy, was noted in 23 patients. One uterus was not palpable and was associated with a "frozen pelvis." Only 2 uteri were considered normal in size, including that of the 15-month-old infant with sarcoma botryoides arising in the upper vagina. Ten patients had a large polypoid mass, frequently necrotic, protruding through the introitus. It is of interest to note that 7 of these patients' tumors contained malignant muscle elements, either myosarcoma or rhabdomyosarcoma. Only one case was diagnosed correctly preoperatively, and this was on the basis of a large polypoid mass protruding through the cervical os.

Treatment.—In the adult varieties of these tumors it is generally considered best to remove the entire uterus and both tubes and ovaries as a primary mode of therapy. Frequently removal of necrotic polypoid tissue from the cervical canal by a preoperative curettage to facilitate definitive surgery is advisable. There was no experience with complete pelvic lymphadenectomy in this series.

Fig. 12. Fig. 13.

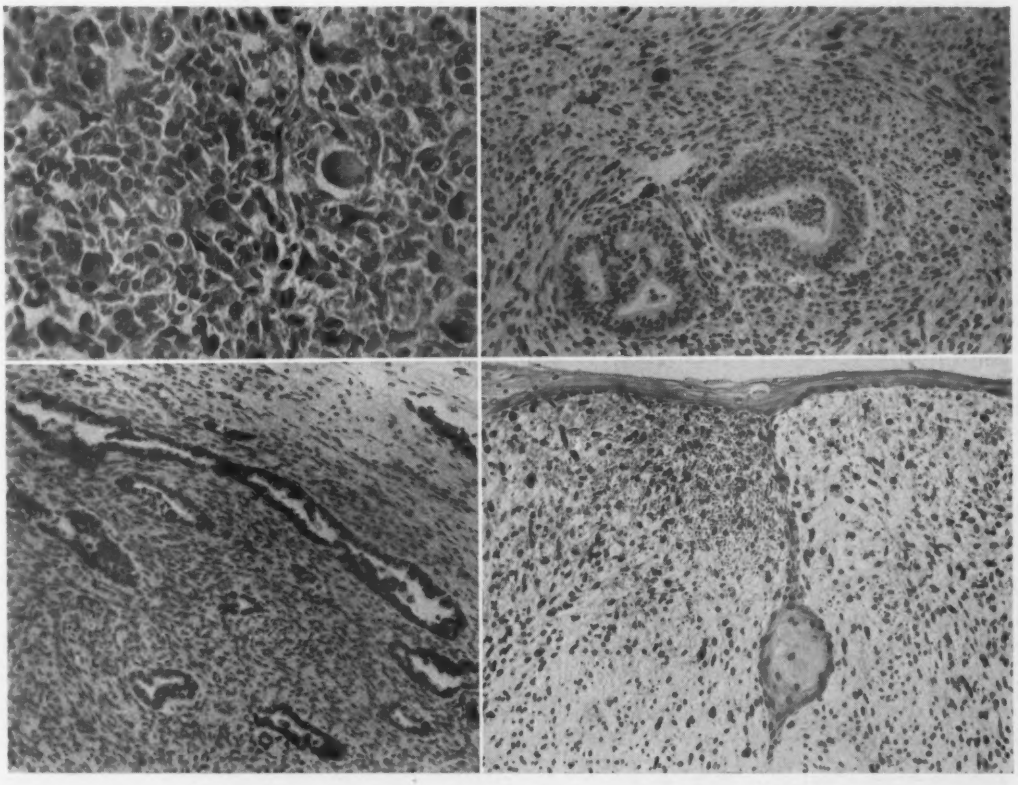


Fig. 14. Fig. 15.

Fig. 12.—Rhabdomyosarcoma. This pure heterologous uterine sarcoma is composed almost entirely of rhabdomyoblasts including straplike cells and racquet-shaped cells with abundant eosinophilic cytoplasm. (×20; reduced ⅓.)

Fig. 13.—Carcinosarcoma. This illustrates the mixed homologous variety with well-differentiated neoplastic glands in a neoplastic stroma composed of fasciculated bipolar cells with occasional bizarre hyperchromatic cells. (×100; reduced ⅓.)

Fig. 14.—Adenocarcinoma metastatic to the ovary at the time of operation. Same case as Fig. 13. (×100; reduced ⅓.)

Fig. 15.—Stromal sarcoma metastatic to suburethral area of vagina one year postoperatively. Same case as Fig. 12. (×100; reduced ⅓.)

One patient with endometrial stromal sarcoma received an intensive course of pelvic x-ray postoperatively and ultimately died with pulmonary

metastases after 11 years. Another patient received intravaginal radium for local recurrence one year following complete surgical treatment, and died 7 years later of a metastatic adenocarcinoma of the breast.

The remaining 2 patients with endometrial stromal sarcoma each had a total hysterectomy with bilateral salpingo-oophorectomy. One patient is alive with suspected recurrent pelvic disease at 9 years; and the other is free of detectable disease at 5 years. The average duration of disease in the 4 patients with endometrial stromal sarcoma is 8 years.

The single patient with stromal endometriosis whose pathologic material was available for study (reported in detail by Corscaden[19]) received a complete cycle of x-ray therapy 3 years following hysterectomy for local recurrence and a frozen pelvis. This tumor ultimately disappeared and the patient eventually died of myelogenous leukemia 11 years following the diagnosis of her uterine neoplasm. Fig. 16.

Only one patient with a pure heterologous mesenchymal sarcoma was encountered in this series. It is an example of rhabdomyosarcoma of the corpus uteri, histologically of the pleomorphic type described by Horn and Enterline.[22] She is alive with radiologically demonstrated pulmonary metastases following palliative hysterectomy with bilateral salpingo-oophorectomy. Operation was performed to relieve abdominal pain and discomfort secondary to a large hematometra and to prevent a potential uterine hemorrhage.

Of the 16 patients with carcinosarcoma, one had definitive surgical treatment and is alive and well after 3 years. Of the remaining 15 patients 9 received a combination of definitive surgery and radiotherapy, and of these only one patient is alive and well at the end of one year. One died of intercurrent disease at 7 months and the remaining patients survived for an average of 13 months. Only 2 patients in this group were treated by purely surgical methods; one is reported to be alive and well after 7 years; the other died of disease at 4 months. Four patients were treated palliatively by x-ray to the pelvis, all are dead with an average survival time of only 3 months. Fig. 18.

Of the 3 patients with mixed mesenchymal sarcoma, one is alive and well 10 years after total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by a complete cycle of x-radiation to the pelvis. One patient who had a supravaginal hysterectomy and bilateral salpingo-oophorectomy followed by palliative pelvic x-ray therapy for extensive retroperitoneal tumor died one month following operation. Autopsy revealed abundant residual sarcoma containing both smooth and striated neoplastic elements. The third patient in this group presented clinically with a case of advanced papillary cystadenocarcinoma of the ovary; the mixed mesenchymal sarcoma of the uterus was an incidental finding in the surgical specimen. This patient died 10 days postoperatively of peritonitis. Widespread secondary ovarian tumor was found in the peritoneum and in the omentum at laparotomy; autopsy disclosed similar metastatic tumor in the pelvis, retroperitoneal tissues, and diaphragm. Fig. 20.

Only one case of sarcoma botryoides has been encountered to date in this institution. It occurred in a 15-month-old infant who was treated by a total pelvic exenteration (Figs. 34 and 35). Extensive pelvic recurrence was observed 7 months later and confirmed by biopsy. No x-ray therapy was given.

Comment

Analysis of the foregoing observations and data indicates that a distinction should be made between the pure homologous sarcomas and the other

three subclasses of mesenchymal sarcoma, namely, those composed of heterologous tissue and those in which there is admixture of a neoplastic epithelial component with a sarcomatous component, either homologous or heterologous. In general, the pure homologous sarcomas tend to arise in a younger group of women, often premenopausal, and pursue a rather indolent clinical course, exhibiting a restrained growth pattern, a tendency to late metastasis, and

Fig. 16.

Fig. 17.

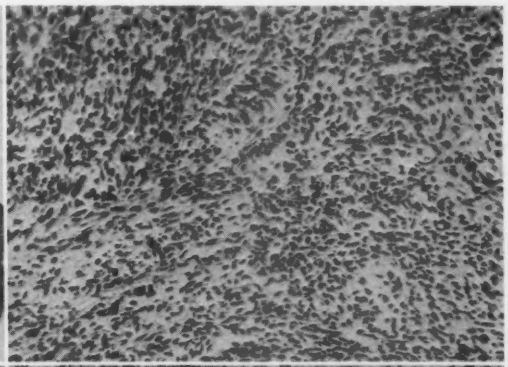


Fig. 18.

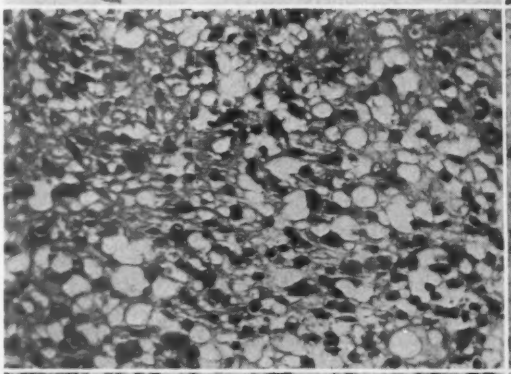


Fig. 19.

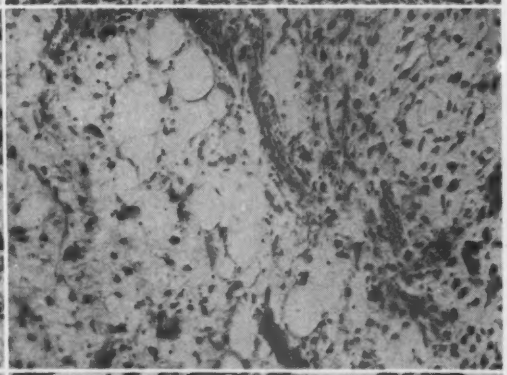


Fig. 20.

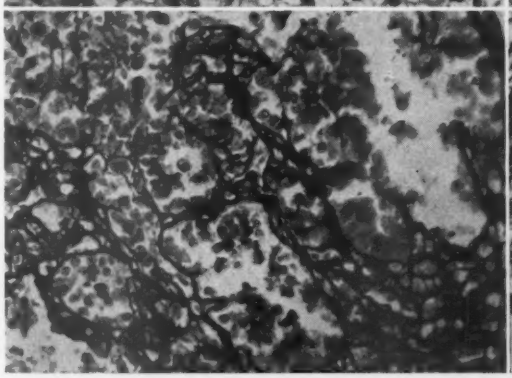


Fig. 21.

Fig. 16.—Collision tumor. Low-power view showing a superficial plaque of stromal sarcoma adjacent to and slightly admixed with a poorly differentiated papillary adenocarcinoma. The adenocarcinoma is seen to infiltrate the myometrium and to appear as a subserosal implant. (×3; reduced ⅓.)

Fig. 17.—Detail of Fig. 16 showing poorly fasciculated pattern of neoplastic stromal cells. (×100; reduced ⅓.)

Fig. 18.—Detail of Fig. 16 showing vacuolation of cells in the stromal sarcoma. (×100; reduced ⅓.)

Fig. 19.—Detail of Fig. 16 showing vacuolation of cells in the stromal sarcoma suggestive of fat. (×200; reduced ⅓.)

Fig. 20.—Collision tumor. Laidlaw's reticulum stain showing clusters of epithelial cells in glandular pattern separated by argyrophilic fibers. (×350; reduced ⅓.)

Fig. 21.—Collision tumor. Laidlaw's reticulum stain showing argyrophilic fibers separating individual cells in an area of stromal sarcoma. (×350; reduced ⅓.)

affording a more favorable prognosis. In contradistinction, the other varieties of mesenchymal sarcoma tend to arise in an older group of women, usually postmenopausal, metastasize rapidly, and afford only limited opportunities for surgical extirpation with hope of cure.

With respect to the pure homologous sarcomas, our observations as well as those of others, notably Park,[24] the excellent and highly informative series of articles by Hunter and his associates,[25-29] and a recent communication by Stearns,[30] indicate a morphologic continuum of stromal proliferation as follows:

1. Simple stromal hyperplasia
2. Instances of adenomyosis with herniation of stromal tissue into lymphatic channels without other clinical or morphologic evidence of aggressive growth
3. Discrete nodular tumors of endometrial stroma which are clinically and morphologically innocuous[30]
4. Concurrent and interrelated stromal endometriosis and adenomyosis[29]
5. Stromatous endometriosis, a true neoplasm of endometrial stroma with a characteristic endolymphatic invasive pattern, with a limited capacity for autonomous growth, which may recur locally, and in a small minority of cases may metastasize after many years[24, 27, 28]
6. Frank stromal sarcoma with focal or partial endolymphatic invasive pattern
7. Overt stromal sarcoma, which may be clinically innocuous when polypoid and exophytic, but is capable of wide dissemination when infiltrative

In the present series we have not included examples of stromal hyperplasia, benign stromal nodules, "invasive" adenomyosis, or other histologically benign lesions. Two patients (Figs. 1, 2, and 3) exhibited examples of overt endometrial stromal sarcoma; one of these patients died with clinical evidence of pulmonary metastases 11 years later; the other died of intercurrent breast cancer 8 years later. One patient (Figs. 6, 7, and 8) exhibited a transition from a diffuse stromal sarcoma to an endolymphatic invasive pattern and is alive 5 years after hysterectomy. One patient exhibited typical stromatous endometriosis (Figs. 9, 10, and 11); the endolymphatic pattern repeated itself in an abdominal scar metastasis 3 years later, and she ultimately died of myelogenous leukemia with no clinical evidence of pelvic disease 15 years after removal of her primary tumor. The fifth patient showed a sarcomatous change in the stroma of an endometrial polyp (Figs. 4 and 5); though lost to follow-up after one year, the exophytic pattern and only superficial myometrial invasion suggested the growth to be innocuous.

Optimal methods of treating patients with pure homologous sarcoma remain uncertain, partly because of the limited number studied intensively to date and partly because of the slow evolution of the behavior pattern of the neoplasm in many instances. Total hysterectomy is sufficient treatment for such forms of stromal growth as simple hyperplasia, "invasive" adenomyosis, benign intramural stromal nodules, "sarcomalike" change in the stroma of endometrial polyps, and the polypoid exophytic type of endometrial stromal sarcoma. In a number of examples of the more aggressive or more extensive varieties of this class of mesenchymal sarcoma, however, surgical extirpation of the growth is not anatomically feasible. In some instances of stromatous endometriosis, the wormlike processes have infiltrated lymphatic channels in the broad ligaments as far as the lateral pelvic walls, and residual tumor is left beyond the planes of resection. Local recurrence is

Fig. 22. Fig. 23.

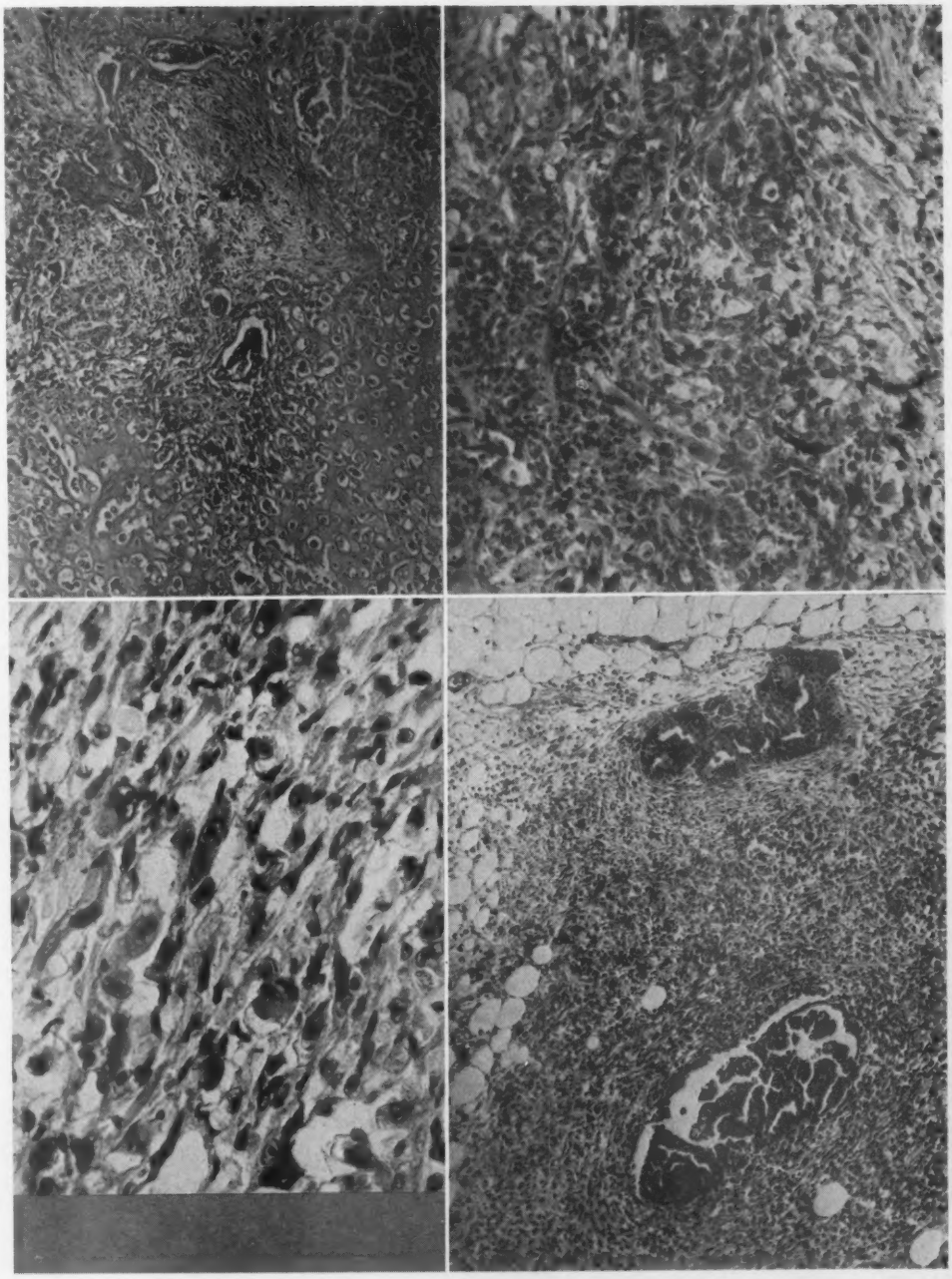


Fig. 24. Fig. 25.

Fig. 22.—Carcinosarcoma, mixed heterologous type. The field contains neoplastic glandular and squamous epithelium as well as cartilage. (×250; reduced ⅙.)

Fig. 23.—Carcinosarcoma, mixed heterologous type. The field contains poorly formed neoplastic glands admixed with rhabdomyoblasts. (×250; reduced ⅙.)

Fig. 24.—Carcinosarcoma, mixed heterologous type. Detail showing rhabdomyoblasts. (×350; reduced ⅙.)

Fig. 25.—Carcinosarcoma, metastatic to omentum. Both neoplastic glands and neoplastic stroma are admixed. Contrast with Figs. 14 and 15, which show dissociation of the two neoplastic components in metastasis. The primary tumor in this case contained a few rhabdomyoblasts. (×100; reduced ⅙.)

to be expected in such instances; x-ray therapy has been of value in diminishing the size of such masses, relieving such conditions as ureteral obstruction, and producing disappearance of metastatic vaginal nodules. The value of x-ray therapy in these circumstances was dramatically exemplified in our single case of stromatous endometriosis and in a similar case reported by Brown and Liber.[21] Henderson[31] recommended total abdominal hysterectomy followed by pelvic irradiation and has shown a long-term survival in 5 cases despite incomplete surgical extirpation of the growth. The efficacy of x-ray therapy may be variable as has been emphasized by Goodall,[32] Park,[24] and Symmonds and Dockerty.[16]

In younger women, in whom the growth is confined to the surgical limits of the uterus, it may not be necessary to remove the tubes and ovaries; metastasis to these structures has not been reported nor is there evidence that ovarian secretions exert a growth-promoting effect on the stromal neoplasm. The plan of management must be based on the idea that the majority of these lesions are "low-grade" malignancies whose clinical behavior is difficult to

Fig. 26. Fig. 27.

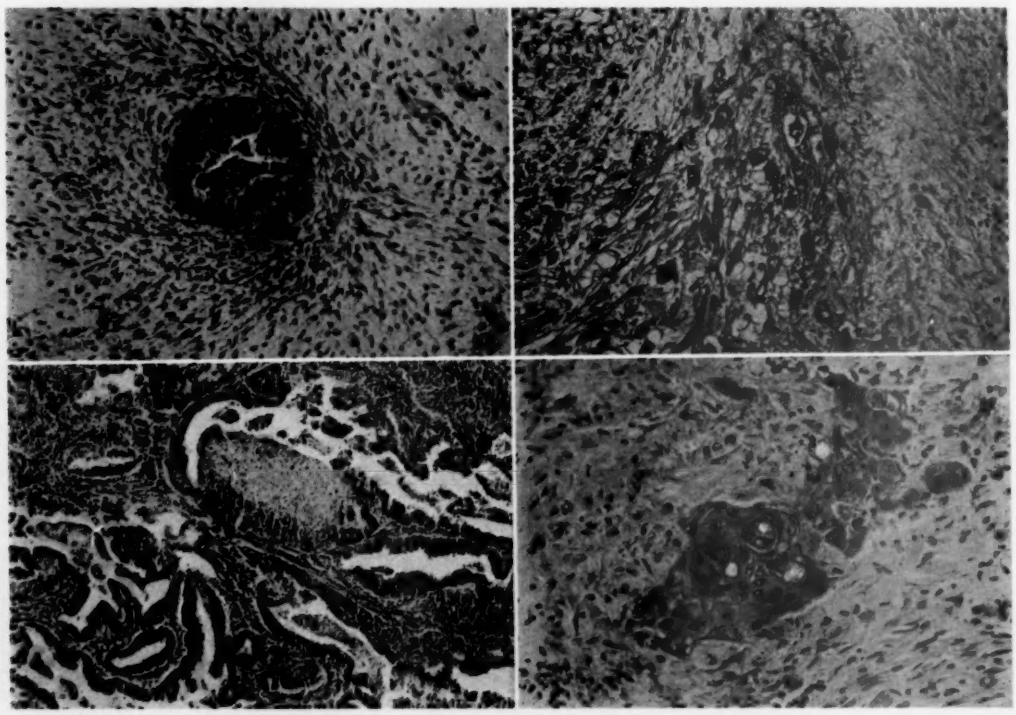


Fig. 28. Fig. 29.

Fig. 26.—Carcinosarcoma, mixed heterologous type. Biopsy of mass protruding through cervical os, showing neoplastic epithelial structure surrounded by a poorly defined lamina of concentrically dispersed mesenchymal cells, mimicking the structure of the embryonic Müllerian apparatus. (×125; reduced 2/7.)

Fig. 27.—Carcinosarcoma, mixed heterologous type. Same biopsy as Fig. 26, showing area of rhabdomyoblasts differentiating from a mesenchymal matrix. (×125; reduced 2/7.)

Fig. 28.—Carcinosarcoma, mixed heterologous type. Second biopsy of same tumor as in Figs. 26 and 27, showing adenocarcinoma with a squamous component. (×55; reduced 2/7.)

Fig. 29.—Carcinosarcoma, mixed heterologous type. Nest of squamous carcinoma in irradiated pelvic mass at autopsy. (×100; reduced 2/7.)

predict accurately on histologic grounds alone. It is inherent in the management of these patients that they be followed at frequent intervals over as long a period of time as possible.

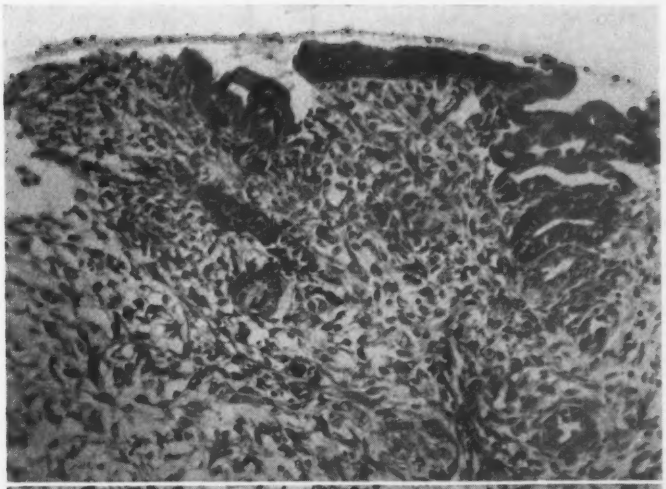


Fig. 30.

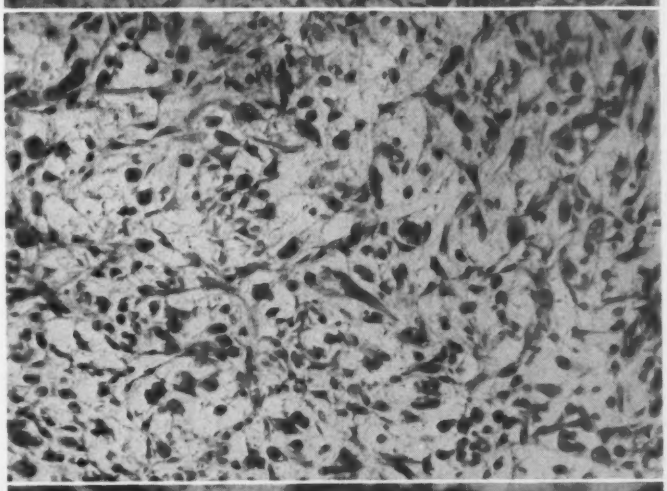


Fig. 31.

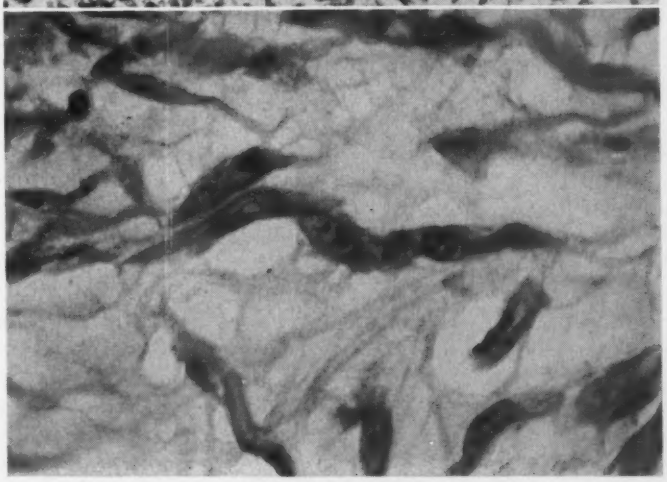


Fig. 32.

Fig. 30.—Carcinosarcoma, mixed heterologous type. Same tumor as in Figs. 26-29 transplanted to subcutaneous tissue of a rat, showing growth of a small amount of glandular component. (×100; reduced ⅓.)

Fig. 31.—Fourth generation subcutaneous transplant in conditioned weanling rat of carcinosarcoma in Fig. 30. The glandular component has been obliterated by an overgrowth of a pleomorphic stromal component in which bipolar straplike cells are prominent. (×100; reduced ⅓.)

Fig. 32.—Fourth generation subcutaneous transplant in conditioned weanling rat of carcinosarcoma in Fig. 30. A long straplike cell with nuclei arranged in tandem is featured. (×400; reduced ⅓.)

With respect to the pure heterologous class of mesenchymal sarcoma, the present series includes one case, a rhabdomyosarcoma (Fig. 12); pulmonary metastases were demonstrated radiologically at the time of prophylactic hysterectomy. Kulka and Douglas[33] have summarized the 20 cases of authentic rhabdomyosarcoma of the uterine corpus in the literature; most cases proved fatal in a few months; a few patients are reported alive at one year but have not been followed longer. Likewise, the reported cases of chondrosarcoma[34-36] and osteosarcoma[37, 38] have all been rapidly fatal. These tumors are all rare and not curable by present methods of therapy.

In this series as well as in others, the mixed tumors, consisting of carcinosarcoma, mixed mesenchymal sarcoma, and botryoid sarcoma, the overwhelming majority of patients are dead of the disease within 2 years. Local recurrence and distant dissemination are the rule, and in many cases it is evident at laparotomy that treatment can be only palliative. To some extent, prognosis depends upon early diagnosis. Analysis of the 16 carcinosarcomas, 3 mixed mesenchymal sarcomas, one rhabdomyosarcoma, and one sarcoma botryoides in this series (i.e., excluding the 5 pure homologous sarcomas) reveals that, of these 21 patients, 14 are now dead and 7 are alive at the time of reporting. Of the 14 patients who are dead, the average duration of symptoms prior to treatment was 9.6 months and the average survival time was 8.2 months; of the 7 surviving patients, the average duration of symptoms prior to treatment was only 2.3 months and the average survival time to date is 39.6 months. Sternberg and associates[15] reported a similar experience. Their 21 patients were all dead at the time of reporting and had an average duration of symptoms of 11.7 months and an average survival time of 8.4 months.

Perhaps of greater importance for prognosis is the anatomic extent of disease at the time of initial therapy, particularly in respect to the depth or extent of myometrial invasion. This information was lacking in a significant number of our cases and we were unable to relate this feature to ultimate outcome. Thiery and Brunschwig,[39] however, have emphasized this point. In 3 of their 9 treated patients the tumor either was limited to the endometrium or invaded the myometrium only superficially; these 3 patients were alive and well without evidence of recurrence 1 to 3½ years later. Of the remaining 6 patients, all had deep myometrial invasion or parametrial extension at the time of operation; 5 of these patients were dead at the time of reporting and one was alive at one year with recurrent disease. Symmonds and Dockerty[16] reported a similar experience with 5 patients whose carcinosarcomas invaded the myometrium deeply and were all dead in an average of 13 months following therapy and 3 patients with polypoid or superficially invasive growths who were alive and free of disease at 1½, 5, and 9½ years, respectively.

It is apparent that considerable information can be gained from careful pathologic study of the tissues removed at operation. The major differences in prognosis depend upon accurate classification of the tumor and careful evaluation of its anatomic extent. While it is unlikely that any of the varieties of pure homologous sarcoma would be confused on microscopic examination with a carcinosarcoma, or a botryoid sarcoma in an infant, or a pure heterologous sarcoma, it is possible to overlook sporadic foci of heterologous elements in a bulky polypoid growth which would necessitate classifying the lesion as a mixed mesenchymal sarcoma. The only safeguard against such an oversight is adequate sampling from multiple areas and the use of a variety of special stains to delineate such histologic details as chondroid matrix, transverse striations, and the like. By the same token, it is important to sample adequately even cases of apparently pure endometrial adenocarcinoma for the presence of scattered areas of sarcomatous stroma.

In the usual series of pure adenocarcinomas one may expect at least a 50 to 60 per cent 5 year survival rate if not better; in carcinosarcoma, the 5 year survival rate is less than 10 per cent. Apparently, even a small amount of sarcoma can imply a significant difference in prognosis. It is evident that the depth of myometrial penetration can be only estimated by sections which are carefully oriented and which extend from the endometrial lining through the entire thickness of the uterine wall, either to the serosa or to the lateral plane of resection.

At present, the optimal therapy which can be offered to a patient with one of the mixed varieties of uterine sarcoma, whether homologous or heterologous, is complete removal of the uterus and adnexa followed by supervoltage radiation of the pelvis. Though an occasional patient may survive for a long interval, the over-all results are discouraging. There is no report of a 5 year survival following radiation therapy alone. In the series reported by Sternberg[15] 10 patients received radiation therapy alone and had a mean survival time of 10 months; 11 patients were treated by a combination of surgery and radiation and had a mean survival time of 11.1 months.

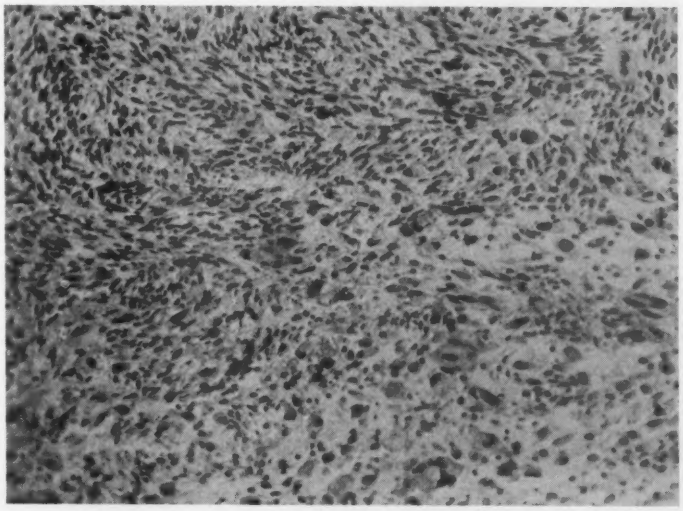


Fig. 33.—Mixed mesenchymal sarcoma. An area of well-fasciculated leiomyosarcoma is seen abutting an area of pleomorphic rhabdomyosarcoma. (×100; reduced ⅛.)

In the series reported by Symmonds and Dockerty,[16] definitive therapy was attempted in 27 of 28 cases. Of the 13 patients treated by surgery followed by x-ray therapy, 8 died with a mean survival time of 17.5 months, and 5 were alive at the time of reporting, one for almost 20 years, one for 15 years, one for over 5 years, and 2 for shorter intervals. Of the 14 patients treated by surgery alone, 9 died with a mean survival time of 10.7 months, and 5 were alive at the time of reporting, one for 18 years, 2 for almost 10 years, and 2 for about one month. Of the 27 treated patients, 5 (18.5 per cent) survived for more than 5 years, but the remainder either died soon after treatment or are indeterminate. These represent the most favorable results obtained in any single series.

Of the 20 patients with mixed uterine sarcomas in the present series, 18 were treated and followed. Ten patients were treated by operation and radiation of whom 8 are now dead with a mean survival time of 10.9 months; 2 are alive and well, at intervals of one year and 10 years. Four patients received palliative radiation following histopathologic diagnosis and all are dead with a mean survival time of 7 months. Four patients were treated by

surgery alone; one died in the postoperative period; one died at one year, and 2 are living, 1½ and 7 years later.

It is our impression that the occasional patient who survives does so because the neoplasm has been extirpated before it has penetrated the uterine wall to any great extent. We concur with the opinion of Symmonds and Dockerty[16] that prognosis cannot be correlated with the histologic grade of malignancy.

Fig. 34.

Fig. 35.

Fig. 34.—Sarcoma botryoides vaginae puellae. Surgical specimen showing the single grapelike polyp that presented clinically at the introitus.

Fig. 35.—Sarcoma botryoides vaginae puellae. Surgical specimen (exenteration) showing complex polypoid grapelike growth arising from the posterior vaginal wall. The rectosigmoid is to the right, the uterus and adnexa above, and the bladder to the left.

It is of interest that of the 28 cases reported by Symmonds and Dockerty,[16] 9 (30 per cent) had received a radiation menopause at an average of 10 years prior to the development of their sarcoma. We were able to find only 1 such patient in our series, and Sternberg and co-workers[15] found none in 21 cases. The role of previous radiation in the pathogenesis of mixed uterine sarcomas awaits further clarification.

Conclusions

1. Twenty-six cases of mesenchymal sarcoma of the uterus are reported, 25 with follow-up, and the results analyzed.

2. The tumors are classified in four categories, according to whether their cellular components are pure or mixed and homologous or heterologous in origin.

3. Irrespective of cell composition, all members of this family of tumors can be traced to an origin from derivatives of the mesenchyme of the urogenital ridge, specifically that derived from and surrounding the epithelium of the Müllerian duct.

4. The historical controversy regarding the nature of these tumors and the role of tissue malformations in their genesis is discussed.

5. The pure homologous sarcomas occur in younger women, often premenopausal, grow slowly, metastasize late if at all, and pursue an indolent clinical course. Total hysterectomy followed by radiation therapy as indicated affords a reasonable prognosis for long-term survival.

6. The pure heterologous sarcomas and the mixed sarcomas, whether homologous or heterologous, occur in older women, usually postmenopausal, grow rapidly, metastasize widely, and afford limited opportunities for treatment with hope of cure. Over 50 per cent of patients with these varieties of sarcoma die within 2 years, and less than 10 per cent can be listed as 5 year survivals. The majority of survivors in this group have tumors which are polypoid, exophytic, and invade the underlying myometrium superficially if at all.

7. Metastases in cases of carcinosarcoma are usually of the carcinomatous component. In one patient the metastasis contained admixed carcinomatous and sarcomatous components. In another patient there was dissociation of the cellular components in the metastases, the ovary containing metastatic adenocarcinoma and a vaginal nodule containing pure metastatic sarcoma.

8. In 10 of 25 cases in adults a prominent clinical feature was the presence of a large polypoid mass protruding through a dilated cervical os in a postmenopausal woman whose presenting symptom was uterine bleeding.

9. To some extent, length of survival is correlated with duration of symptoms prior to treatment. Excluding the pure homologous sarcomas, in 14 patients who are dead the average duration of symptoms was 9.6 months and the average survival time was 8.2 months; in 7 patients alive at the time of reporting the average duration of symptoms was 2.3 months and the average survival time was 39.6 months.

10. Treatment of patients with carcinosarcoma or mixed mesenchymal sarcoma must depend upon the extent of the disease at the time of diagnosis.

If the tumor is polypoid and confined to the endometrium or has only superficially invaded the myometrium, total abdominal hysterectomy with bilateral salpingo-oophorectomy is sufficient. With extension beyond these limits, the prognosis is generally poor, and a course of supervoltage radiation to the pelvis for palliative purposes is indicated. No results are reported with cases treated by radical hysterectomy, exenterative surgery in adults, or chemotherapeutic compounds. The prognosis appears to be hopeless in the presence of extrapelvic disease.

We acknowledge with gratitude the courtesy of Dr. Edith Sproul in making available the cases from the Francis Delafield Hospital. Also acknowledged with thanks is the loan of original pathologic material by Dr. William E. Finkelstein, Polyclinic Hospital, New York, Dr. Alfred W. Schwartz, Jewish Memorial Hospital, New York, and Dr. Harold Liepow, Lincoln Hospital, New York. In addition, thanks are due to Dr. Dorothy H. Anderson, Babies' Hospital, New York, New York, to Dr. Adolph B. Clachko, Hackensack, New Jersey, and to Dr. O. V. Angstlich, Port Said, Egypt, for contributing unusual cases.

References

1. Ober, W. B.: Ann. New York Acad. Sc. (In press.)
2. Novak, E., and Anderson, D. F.: Am. J. Obst. & Gynec. **34**: 740, 1937.
3. MacFarlane, K. T.: Am. J. Obst. & Gynec. **59**: 1304, 1950.
4. Webb, G. A.: Obst. & Gynec. **6**: 38, 1955.
5. McFarland, J.: Surg. Gynec. & Obst. **61**: 42, 1935.
6. Gruenwald, P.: Anat. Rec. **81**: 1, 1941.
7. Gruenwald, P.: Arch. Path. **35**: 53, 1943.
8. Pfannenstiel, J.: Virchows Arch. path. Anat. **127**: 305, 1892.
9. Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, 1906, Fischer, vol. 1.
10. Albrecht, E.: Verhandl. d. deutsch. path. Gesellsch. **7**: 153, 1904.
11. Nicholson, G. W.: Guy's Hosp. Rep. **69**: 173, 1918.
12. Willis, R. A.: Pathology of Tumours, ed. 2, London, 1953, Butterworth & Co., Ltd., chap. 48.
13. Zenker, F. A.: Ueber die Veränderungen der willkührlichen Muskeln in abdominalis: Nebst einem Excurs über die pathologische Neubildung quergestreiften Muskelgewebes, Leipzig, 1864, F. C. W. Vogel, pp. 84-86.
14. Alznauer, R. L.: Arch. Path. **60**: 329, 1955.
15. Sternberg, W. H., Clark, W. H., and Smith, R. C.: Cancer **7**: 704, 1954.
16. Symmonds, R. E., and Dockerty, M. B.: Surg. Gynec. & Obst. **100**: 232, 322, 1955.
17. Meyer, R.: Zentralbl. allg. Path. u. path. Anat. **30**: 291, 1919.
18. Corscaden, J. A., and Singh, B. P.: Am. J. Obst. & Gynec. **75**: 149, 1958.
19. Corscaden, J. A.: Trans. Am. A. Obst., Gynec., & Abd. Surgeons **61**: 66, 1950.
20. Watson, B. P.: Am. J. Obst. & Gynec. **45**: 1025, 1943.
21. Brown, C. R., and Liber, A. F.: New York J. Med. **42**: 161, 1942.
22. Horn, R. C., Jr., and Enterline, H. T.: Cancer **11**: 181, 1958.
23. Stout, A. P.: Ann. Surg. **118**: 445, 1943.
24. Park, W. W.: J. Obst. & Gynaec. Brit. Emp. **56**: 759, 1949.
25. Robertson, T. D., Hunter, W. C., Larson, C. P., and Snyder, G. A. C.: Am. J. Clin. Path. **12**: 1, 1942.
26. Hunter, W. C., Smith, L. L., and Reiner, W. C.: Am. J. Obst. & Gynec. **53**: 663, 1947.
27. Hunter, W. C.: Surgery **34**: 258, 1953.
28. Hunter, W. C., Nohlgren, J. C., and Lancefield, S. M.: Am. J. Obst. & Gynec. **72**: 1072, 1956.
29. Hunter, W. C., and Lattig, G. J.: Am. J. Obst. & Gynec. **75**: 258, 1958.
30. Stearns, H. C.: Am. J. Obst. & Gynec. **75**: 663, 1958.
31. Henderson, D. N.: Am. J. Obst. & Gynec. **52**: 1000, 1946.
32. Goodall, J. R.: J. Obst. & Gynaec. Brit. Emp. **47**: 13, 1940.
33. Kulka, E. W., and Douglas, G. W.: Cancer **5**: 727, 1952.
34. Hartfall, S. J.: J. Obst. & Gynaec. Brit. Emp. **38**: 593, 1931.
35. Peña, E. F.: Am. J. Obst. & Gynec. **61**: 461, 1951.
36. Ober, W. B.: Unpublished data.
37. Stier, R. F. E., and Lyman, J. C.: Am. J. Clin. Path. **6**: 562, 1936.
38. Scheffey, L. C., Levinson, J., Herbut, P. A., Hepler, T. K., and Gilmore, G. H.: Obst. & Gynec. **8**: 444, 1956.
39. Thiery, M., and Brunschwig, A.: Acta obst. et gynec. scandinav. **34**: 301, 1955.

THE HISTOGENESIS OF CARCINOSARCOMA (MIXED MESODERMAL TUMOR) OF THE UTERUS AS REVEALED BY TISSUE CULTURE STUDIES*

ALAN RUBIN, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and The Gynecean Hospital Institute for Gynecologic Research of the School of Medicine and Hospital of the University of Pennsylvania)

THE histogenesis of carcinosarcoma is obscure. Indeed, in the past, opinions have varied as to whether this tumor, more properly designated as a mixed mesodermal tumor, actually was a pathologic entity.[1, 8] Most authors, however, are now convinced that in some instances both carcinomatous and sarcomatous elements can be found coexisting in the uterus in which the possibility of the mere collision of two separate tumors can be reasonably well excluded.[2-10] They cite the presence of sarcomatous striated muscle cells or striated rhabdomyoblasts, or small acidophilic granules in immature rhabdomyoblasts, in conjunction with carcinoma, as being useful in the diagnosis.[2] The presence of both carcinoma and sarcoma in the same metastatic lesion is given as final proof.[2] The typical clinical picture of a malignant, polypoid uterine lesion, with frequent, widespread, and early metastases, and a rapidly fatal termination, in contrast to the slower course of endometrial carcinoma, is given as ancillary clinical support. On the other hand, so eminent a pathologist as Willis denied the existence of carcinosarcoma.[1] The renowned Ewing[11] stated that many such tumors are actually an atypical growth of carcinoma cells. He pointed out that metastases are usually carcinomatous. He suggested that the exudation and inflammation accompanying tumors of the endometrium greatly favor the growth of atypical cells.

Because of these divergent points of view, the study of carcinosarcoma grown in tissue cultures, where elements of exudation, inflammation, compression of cells, vascularity, tumor bed, host response, and so on, are absent, seemed to be a logical technique for attempting to learn more about such tumors. Accordingly, a tumor which exhibited all the gross, microscopic, and clinical characteristics ascribed to carcinosarcoma was grown in tissue culture. To the best of our knowledge the growth of human carcinosarcoma in tissue culture has not previously been reported.

Case Report

Mrs. E. H., a 57-year-old Negro para ii, gravida ii, was admitted to the hospital because of 6 weeks of profuse vaginal bleeding. There had been a 20 pound weight loss over

*Aided in part by a grant from the University Cancer Research Fund, and by the Dr. Alan Rubin Research Fund.

the past 3 months. The patient had had a left radical mastectomy for carcinoma 7 years previously. She had then been given an x-ray menopause. She had remained free of any evidence of recurrence. The physical examination on admission disclosed a well-healed radical mastectomy scar with no evidence of recurrence of disease. Pelvic examination showed the cervix to be dilated 4 cm. by an irregular, friable, bleeding mass which protruded from the os. No definite pedicle to the mass could be ascertained. The uterus was firm and symmetrically enlarged to the size of a 4 months' gestation. The adnexa were not palpable. The protruding mass was biopsied and a diagnosis of carcinosarcoma obtained. A thorough medical investigation disclosed only microcytic anemia and diabetes mellitus. A total hysterectomy and bilateral salpingo-oophorectomy were performed. No gross evidence of metastasis was found.

Pathological Report.—The uterus weighed 680 grams. The wall was 1.5 cm. in thickness. The endometrial cavity was 8 cm. in length. The cavity had been completely replaced by a necrotic, polypoid, friable tumor mass which protruded beyond the external cervical os. The uterus was distorted by several 2 to 3 cm. soft tumor masses which were intramural. The cervix was necrotic, poorly epithelized, and not easily identified. The tubes were adherent to the ovaries. Their fimbriae were closed. The ovaries appeared normal.

Microscopic.—Sections of the cervix showed no recognizable stratified epithelium. There was almost complete replacement by tumor cells which were large and bizarre, often with a striking eosinophilia of the cytoplasm (Fig. 1). Elongated, straplike or ribbonlike cells with cross-striations were noted (Figs. 2 and 3). The nuclei were large and irregular. Many areas showed epithelial conformations (Figs. 1 and 2) of a poorly differentiated carcinoma. The body of the uterus showed the same type of tumor cells. Very free invasion of the myometrium and blood vessels was apparent. No endometrium was recognizable. No evidence of separate carcinoma or sarcoma could be found. Nothing resembling mammary carcinoma or the original breast lesion was seen.

Sections of the tubes showed obliteration and fibrous tissue replacement of the mucosa. Sections of the ovaries showed only increased hyalinized connective tissue.

Diagnosis.—Carcinosarcoma (mixed mesodermal tumor) of the uterus; chronic salpingitis, bilateral. Ovary, bilateral.

The patient had an uneventful postoperative course.

Follow-up.—One month postoperatively, abdominal, pelvic, and rectal examinations were negative except for the presence of a slightly reddened area 1 cm. in diameter approximately 2 cm. from the apex of the vaginal vault. Two and one-half months postoperatively the patient complained of vomiting and weight loss. Large abdominal masses were palpable. In mid-vagina there were several 3 to 4 cm. friable, polypoid lesions. A similar mass protruded from the urethral meatus. Biopsies of the vaginal and urethral tumors were used to prepare tissue cultures and microscopic sections. The microscopic picture was identical with that of the original uterine lesion. The patient was readmitted and given a course of nitrogen mustard intravenously. The abdominal mass appeared to grow smaller. No effect upon the urethral or vaginal lesions was noted. She was discharged after 2 weeks. She was readmitted in a terminal state one month later (4 months after hysterectomy) and died of pulmonary edema. Autopsy showed large tumor masses of the abdomen, pelvis, vagina, and urethra. There were also metastases to the pleura, lungs, vertebral bone marrow, and periaortic, mediastinal, and cervical lymph nodes. All sections of the metastatic deposits revealed tumor identical with that of the original uterine lesion.

Tissue Cultures

Technique.—Portions of the tumor were secured from metastases which appeared in the vagina and urethral meatus 10 weeks after the hysterectomy. All presented the gross

---

Fig. 1.—Elongated, straplike cells of sarcoma intermingled with epithelial conformations of carcinoma. (×290; reduced ¼.)

Fig. 2.—Higher-power view of field outlined in Fig. 1. Note elongated, straplike sarcoma cells with granular cytoplasm and cross-striations (better seen in Fig. 3), and epithelial conformation of irregular carcinoma cells with bizarre nuclei. (×700; reduced ¼.)

Fig. 3.—Elongated, straplike or ribbonlike cells with cross-striations and nuclei in tandem. (×1,500; reduced ¼.)

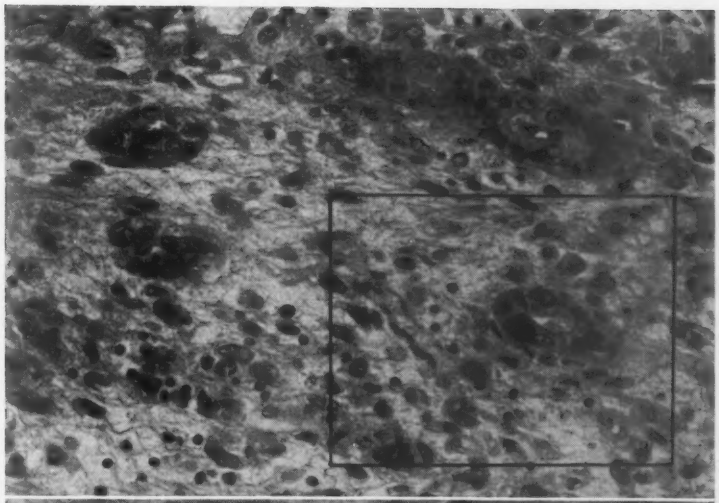


Fig. 1.

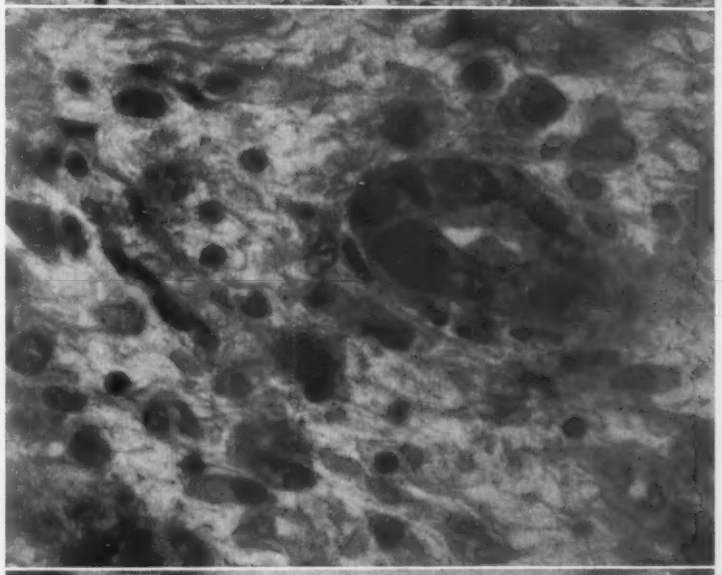


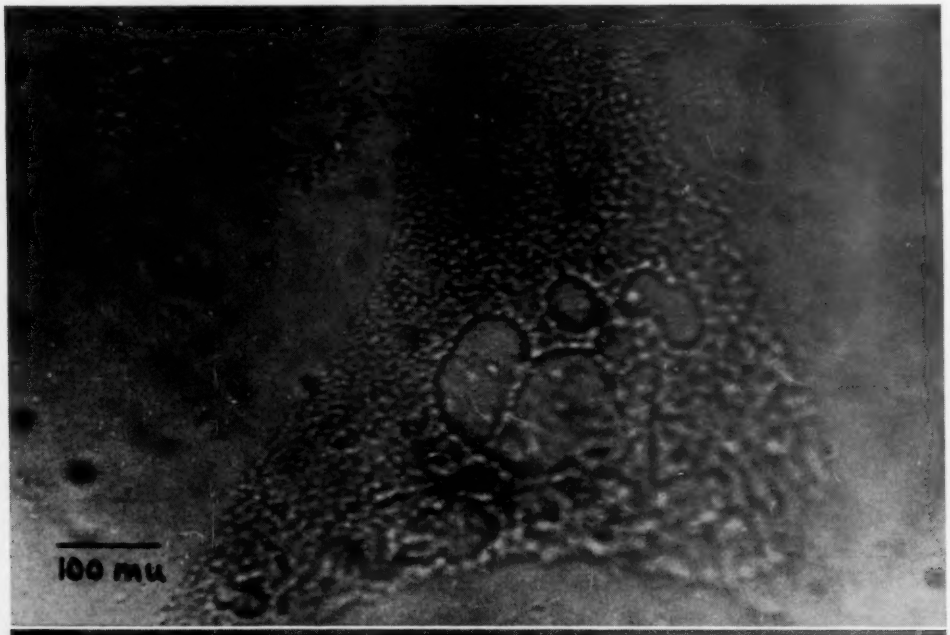
Fig. 2.

Fig. 3.

Figs. 1-3.—*For legends see opposite page.*

and microscopic characteristics of the original uterine lesion. Aliquots of the tumors were made into paraffin sections and stained with hematoxylin and eosin or phosphotungstic acid and hematoxylin to demonstrate cross-striations in muscle cells. Portions of the tumors were made into hanging-drop tissue cultures.[12, 13] The medium for the tissue cultures consisted

Fig. 4.



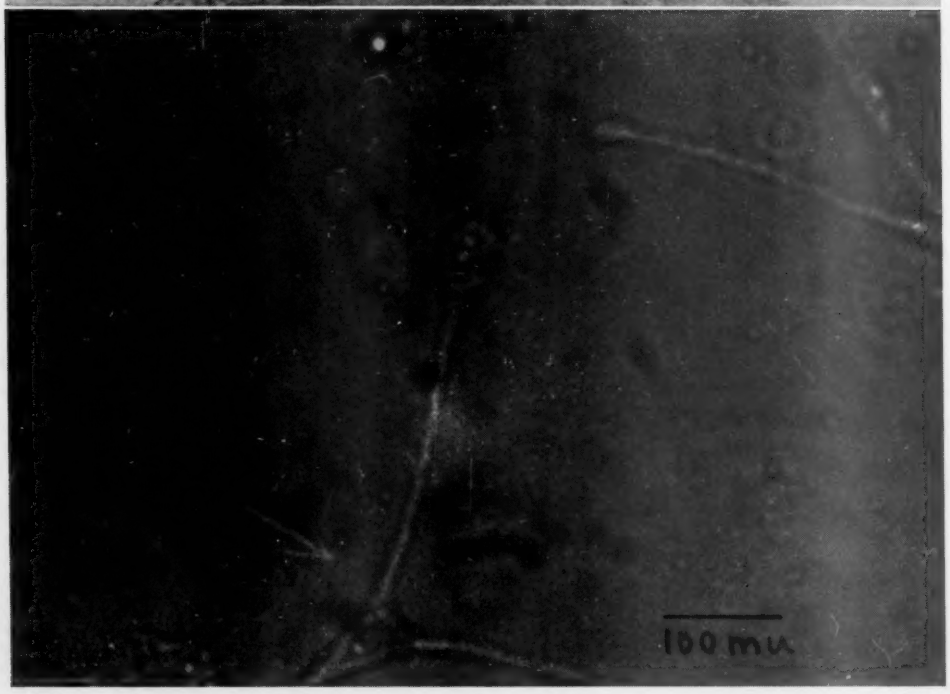


Fig. 5.

Fig. 4.—Carcinoma cells from carcinosarcoma growing in 19-day-old tissue culture. Note large, flat, squamous type of cells with vacuolated cytoplasm and large, bizarre nuclei.

Fig. 5.—Sarcomalike cell from same 19-day-old tissue culture as in Fig. 4. Note large, elongated cell with oval nucleus and bulbous end to process.

of 6 ml. of Gey's solution[14] and 6 ml. of chick embryo extract (1 part 9 to 10 day chick embryo to 2 parts of Gey's solution). To this mixture were added 0.001 Gm. potassium penicillin G and either equal parts of horse serum or 15 drops of human placental serum.[15] The tumor tissue in this medium was added to a drop of chicken plasma. Cultures were incubated at 37° C. At 2 to 3 day intervals the medium was removed by aspiration and fresh medium instilled. Neutral red was added to some cultures to aid in the determination of viability of cells.[12]

Observations.—Beginning in 48 hours, 2 types of cells were seen to migrate from the explants. One was large, polyhedral, with granular cytoplasm, and a round nucleus or nuclei (Fig. 4). The cells varied somewhat in shape and often had large, bizarre nuclei which were frequently multiple. The cells tended initially to grow out in sheets, and then to separate into individual cells. These were considered to be malignant epithelial cells, that is, carcinoma. Cells of the second type were thin, with long processes and one or more oval nuclei (Fig. 5). These cells differed from benign fibroblasts in that they were larger, with bizarre nuclei of varying size, shape, and number, and sometimes had bulbous-appearing ends to their processes. These were thought to be malignant connective tissue cells, that is, sarcoma. Stained preparations of these cells were made, but they were of poor quality, and cross-striations could not be demonstrated. Tissue cultures of the vaginal and urethral lesions both exhibited the same features. Macrophages and lymphocytes were also seen scattered throughout the cultures. The explants gradually died over a 2 week interval.

Comment

Although the original tumor and the metastases fulfilled all the criteria required by those who consider carcinosarcoma a pathologic entity, those who are skeptical about such a diagnosis might say that the sarcomatous-appearing cells were really carcinoma cells resembling sarcoma. In tissue culture, however, there were two distinct cell types. No intermediate cell types were seen in the tissue cultures, or any evidence of transition from carcinoma to sarcoma-like cells, as Novak[10] said can usually be found on careful study of sections of most tumors thought to be carcinosarcoma, but which often really are just atypical carcinomas. Thus, Virchow's[16] original concept may well be correct, namely, that carcinosarcomas are manifestations of the multipotentiality of the mother tissue and that "sarcoma and carcinoma grow side by side like two branches of the same tree."

Tissue culture techniques might also be useful in differentiating carcinosarcoma from a pleomorphic or degenerating endometrial carcinoma. Their clinical value is manifest when it is realized that carcinosarcoma usually connotes radioresistance, rapid recurrence, metastasis, and early death, compared with the generally slower course of even an anaplastic endometrial carcinoma.

Summary

A case of carcinosarcoma (mixed mesodermal tumor) of the uterus with the classical clinical and histologic picture is presented.

The first description of human carcinosarcoma grown in tissue culture is given. In tissue cultures of the tumor two distinct cell types were distinguished. One cell type had the characteristics of carcinoma, the other, of sarcoma. No intermediate cell types or evidence of transition from one form to the other was

seen. These observations lend support to the thesis that carcinosarcoma is a distinct pathologic entity in which carcinomatous and sarcomatous elements coexist, rather than merely an atypical or pleomorphic carcinoma.

Addendum.—Shortly before the galley proof of this article was received, Papanicolaou and Maddi[17] reported the growth in tissue culture of a carcinosarcoma of the uterus. The character of the malignant cells in vitro was thought to indicate a stromal origin.

References

1. Willis, R. A.: Pathology of Tumours, London, 1948, Butterworth Medical Publications.
2. Hill, R. P., and Miller, F. N., Jr.: Cancer **4**: 803, 1951.
3. Corscaden, J. A.: Am. J. Obst. & Gynec. **61**: 743, 1951.
4. Hardy, J. A., and Moragues, V.: Am. J. Obst. & Gynec. **63**: 307, 1952.
5. McLetchie, N. G. B., and Reynolds, D. P.: Am. J. Obst. & Gynec. **65**: 1123, 1953.
6. Hall, J. E., and Nelms, W. F.: Am. J. Obst. & Gynec. **65**: 433, 1953.
7. Klein, J.: Am. J. Obst. & Gynec. **65**: 1212, 1953.
8. MacFarlane, K. T., and Pritchard, J. E.: Am. J. Obst. & Gynec. **68**: 652, 1954.
9. Sternberg, W. H., Clark, W. H., and Smith, R. C.: Cancer **7**: 704, 1954.
10. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company.
11. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4. Philadelphia, 1940, W. B. Saunders Company.
12. Rubin, A., Springer, G. F., and Hogue, M. J.: Cancer Res. **14**: 456, 1954.
13. Rubin, A., Springer, G. F., and Hogue, M. J.: Anat. Rec. **118**: 2, 1954.
14. Gey, G. O., and Gey, M. K.: Am. J. Cancer **27**: 45, 1936.
15. Hogue, M. J., and Rubin, A.: Cancer Res. **15**: 462, 1955.
16. Virchow, R.: Die Krankhaften Geschwuelste, vol. 2, Berlin, 1864, August Hirschwald.
17. Papanicolaou, G. N., and Maddi, F. V.: Am. J. Obst. & Gynec. **76**: 601, 1958.

MIXED MESODERMAL TUMORS

A Report of 11 Cases

L. C. Marcella, M.D., and J. Keith Cromer, M.D.,
Washington, D. C.

(From the Department of Obstetrics and Gynecology, Washington Hospital Center)

MIXED mesodermal tumor of the female genital tract is a rare and highly malignant disease. The origin of this tumor is said to be Müllerian, and there is a variable degree of differentiation toward sarcoma of the endometrial stroma and carcinoma of the endometrial glands.[21] The tumor is variously called mixed Müllerian tumor, carcinosarcoma, sarcoma botryoides, or malignant mixed tumor of Müllerian origin. Some authors[2, 18, 32, 33] attempt to differentiate these tumors as separate entities, but admit that mixed mesodermal tumor and carcinosarcoma have identical origins, clinical features, gross appearance, and prognosis. The terms seem to be interchangeable, and even careful histologic techniques cannot always separate these tumors.

A tumor composed of two or more mesodermal elements heterologous to the uterus, such as striated muscle, cartilage, myxomatous tissue, fat, or bone, qualifies as a mixed mesodermal tumor. In the tumors referred to as carcinosarcomas, in which both epithelial and sarcomatous malignant elements are present, it is possible that sufficient sections might reveal other heterologous tissues. Similarly, where only fat, myxomatous tissue, or cartilage is found in connection with sarcoma, further sections may reveal epithelial elements.

There has been no satisfactory explanation given concerning the location of this tumor in the generative tract at different ages. Sarcoma botryoides characteristically is a tumor of the vagina in premenarchal children. The relatively rare mixed tumor of the cervix occurs during active menstrual years, and the fundal tumor is most common after menopause.

Frequency

Hardy and Moragues[11] in 1952 reported 116 cases of mixed tumors of the uterus prior to 1950, and added 2 cases of their own. Referring only to carcinosarcoma, Hofstätter[16] reported that only 16 cases in the world's literature prior to 1953 were acceptable to him and to Chiari. Ahumada[2] reported 11 cases of mixed tumor encountered over a 20 year period, among 27,000 gynecologic admissions, or an incidence of 0.04 per cent. Over a 6 year period Sternberg[31] encountered 21 cases among 26,114 gynecologic admissions, or 0.08 per cent.

Table I lists the cases reported in the world's literature since 1950, and shows a total of 234 cases to the present time.

TABLE I. CASES REPORTED IN WORLD'S LITERATURE SINCE 1950

AUTHOR AND REFERENCE	YEAR REPORTED	NUMBER OF CASES
Hardy and Moragues[11]	Prior to 1950 (Review)	116
Ahumada[2]	1951	11
Hill and Miller[14]	1951	4
Altmann[3]	1952	1
Bruntsch[5]	1952	2
Chesky[7]	1952	1
Hardy and Moragues[11]	1952	2
Lisa[20]	1952	1
Opocher[27]	1952	1
Winter[37]	1952	1
Ahumada[1]	1953	1
Feller[9]	1953	2
Hall and Nelms[10]	1953	1
Hofstätter[15]	1953	1
Klein[19]	1953	8
McCutcheon[24]	1953	1
McLetchie[25]	1953	1
Mossetti[26]	1953	1
Wilson[36]	1953	6
Boschann[4]	1954	1
MacFarlane and Pritchard[21]	1954	2
Sternberg[31]	1954	21
Symmonds and Dockerty[32, 33]	1955	28
Cantor[6]	1956	1
Martin[22]	1956	2
Masubuchi[23]	1956	1
Perovic[28]	1956	1
Skandalakis[17]	1957	2
Karpas[18]	1957	1
Witt[38]	1957	1
Marcella	1958	11
Total		234

During the period from 1941 to 1957 at Garfield Memorial Hospital, 11 cases of mixed mesodermal tumor were treated. These represented 0.07 per cent of the gynecologic admissions during this time. These cases constitute the basis for this report, and are summarized in Table II.

Present Series

Age.—The age range of patients in the present series was from 33 to 65 years, and the median age was 47 years. This is somewhat younger than the median or average age in other reported series, and the usual age of patients with carcinoma of the fundus, which is over 55 years. Of the 11 cases in this series, 9 of the tumors arose in the fundus, one in the cervix, and one in the ovary. The patient whose tumor arose in the cervix was the youngest in the group.

Clinical Features.—Postmenopausal bleeding, or irregularity of menstruation, was the presenting complaint in 10 cases. In Case 2, that in which the tumor arose in the right ovary, diarrhea and abdominal swelling were the initial symptoms. Other complaints were weakness, malaise, anorexia, fatigability, and pressure sensations in the pelvis. Pain was rarely noted, as was weight loss, perhaps because of the rapidity of growth of the tumor. In each case a pelvic examination led to a presumptive diagnosis of genital tract malignancy. A review of several other series of cases indicates a history of previous pelvic irradiation in significant numbers. Klein[19] reported that in one series of 28 cases 11 patients had such a history. In the present series, Case 6 had received radium treatment for vaginal bleeding 6 years prior to admission.

It is of extreme clinical importance to make an early diagnosis of this tumor, and especially to differentiate it from endometrial carcinoma. Both occur chiefly in postmenopausal patients. In contrast to endometrial carcinoma, where late metastasis is the rule, the patients with mixed mesodermal tumors have early metastases, and a more rapid deterioration.

Pathology.—There is extreme variability in the gross and microscopic appearance of the tumor, depending on which heterologous tissues are present. Cartilage, fat, myxomatous tissue, or osteogenic tissue may be recognized grossly. The common microscopic elements are striated myoblasts, immature myoblasts, adenocarcinoma, adenoacanthoma, osteogenic sarcoma, chondrosarcoma, liposarcoma, and fibromyxomatous tissue. Histologically, they are most often confused with anaplastic carcinomas and the various sarcomas. In many cases the metastases consist chiefly of sarcoma. Table III lists the gross description of the tumors, and the location of metastases at autopsy when performed.

Prognosis.—The average life span after diagnosis is less than one year, regardless of the type of therapy used. Table IV lists the reported 5 year survivals in the world's literature to the present time. Of the 10 patients who died in this series, the average survival time was 1 year, 8 months. Immature tissues are said to be radiosensitive, but in most instances these tumors are not sterilized by irradiation. Several types of postoperative irradiation were used, and N,N′N″triethylenethiophosphoramide (thioTEPA) was used in 5 cases, but none of these altered the fatal outcome in the 10 patients.

Case Presentations

Two cases were chosen for detailed presentation because of their unusual nature.

CASE 1.—Patient V. T., a 33-year-old Negro woman, gravida i, para i, was seen in the clinic of Garfield Memorial Hospital on Aug. 23, 1948. She complained of heavy white vaginal discharge of 15 years' duration, which became bloody the year before admission. There was a history of burning on urination and nocturia twice a night. She had received penicillin therapy for syphilis in June, 1948.

On pelvic examination the vagina was filled with a thick, greenish-white discharge. The cervix was replaced by a necrotic, fungating gray tumor measuring 6 by 4 cm. which bled easily on manipulation. The tumor extended out the right vaginal vault and into the right parametrium, but not to the pelvic wall. The fundus was slightly enlarged and was 80 to 90 per cent mobile. The uterosacral area and left parametrium appeared free of disease and the adnexa were negative. The clinical impression was Stage II carcinoma of the cervix.

Laboratory studies showed anemia with a hemoglobin determination of 7.5 Gm. and erythrocyte count of 3.3 million per cubic millimeter.

X-ray studies showed the chest to be normal; a barium enema was normal; an intravenous pyelogram and a cystoscopic examination showed a tumor in the pelvis which pressed on the superior and lateral surfaces of the bladder.

A biopsy of the cervix on Aug. 23, 1948, was reported as mixed mesodermal tumor or anaplastic carcinoma, probably the former. A second biopsy one week later was reported as mixed mesodermal tumor.

Beginning on Sept. 1, 1948, the patient received eight transvaginal x-ray treatments at 140 kv., the total dose 6,400 r over 10 days' time. Pelvic examination at the completion of irradiation showed only slight reduction in the size of the tumor.

On Sept. 24, 1948, a Wertheim hysterectomy was performed. Enlarged discrete nodes were found extending up the iliac vessels to the bifurcation of the aorta.

Gross description: The specimen consisted of a totally resected uterus with attached vaginal cuff and both tubes and ovaries and iliac lymph nodes. There was a yellowish-gray

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Case 1. Typical sarcoma pattern in section of biopsy of cervix, showing giant cells and malignant spindle cells. (Hematoxylin and eosin. ×300; reduced ¼.)

Fig. 2.—Case 1. Another section of biopsy of cervix, showing fat cells. (Hematoxylin and eosin. ×300; reduced ¼.)

Fig. 3.—Case 1. From cervical tumor removed at hysterectomy. Typical sarcoma pattern present in most sections. (Hematoxylin and eosin. ×100; reduced ¼.)

tumor in the cervix, which extended into the body of the uterus for an average distance of 4.4 cm., and through the entire thickness of the wall of the cervix. A cut section through the tumor revealed firm, slightly granular, pinkish-yellow tissue. The endometrium averaged 0.2 cm. in thickness and was dark red and velvety. There were two nodes measuring up to 2.3 cm. in diameter from the right iliac area and four nodes measuring up to 1.7 cm. from the left iliac area.

Microscopic description: Fig. 1 shows the sarcoma pattern of the cervical biopsy taken Aug. 31, 1948. There are giant cells, and elongate spindle cells with blunt, hyperchromatic nuclei showing many mitotic figures, surrounded by a dense connective tissue stroma. Fig. 2 is from another section of the cervical biopsy which shows a large area of fat cells. The finding of sarcoma cells and fat cells in the same tumor established the diagnosis. Fig. 3 is from the tumor of the cervix removed at hysterectomy on Sept. 24, 1948. Most sections revealed only a sarcoma pattern without recognizable irradiation changes.

Microscopic diagnosis: Mixed mesodermal tumor of the cervix with extention to the fundus of the uterus and metastases to the iliac nodes.

Subsequent Course.—On Jan. 20, 1949, 4 months after hysterectomy, left superficial inguinal and left iliac node dissections were performed. There was one minute focus of metastatic sarcoma in one iliac node.

One week later, a right inguinal node dissection was performed. There was a minute focus of metastatic sarcoma in one deep node.

The patient has been followed in the outpatient clinic and has had no further difficulties. At present, 9 years and 7 months after treatment was begun, she is 42 years of age, and works an 8 hour day as a domestic.

CASE 2.—Patient M. M., a 45-year-old white woman, was in apparent good health until July, 1957, when she noted the onset of headaches, weakness, "hot spells," and diarrhea. Two weeks later the abdomen began to swell. The patient was admitted to Providence Hospital on July 30, 1957. She was gravida iii, para iii. The menarche was at 13 years of age and menstrual periods occurred every 26 to 28 days for 4 days. Menstruation was regular prior to admission.

On admission the laboratory data were: hemoglobin 14.1 Gm., hematocrit 43 per cent, erythrocyte count 4.05 million, leukocyte count 8,900. On Aug. 1, 1957, an exploratory laparotomy with total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. At operation a large amount of blood-tinged ascitic fluid was removed. The abdominal organs were not remarkable except for two lengths of intestine which were attached to the ovarian masses. Grossly there was a malignant tumor of the right ovary and a cystic left ovary with attached intestine.

Grossly, the specimen consisted of an ovarian tumor submitted in multiple fragments composed of yellowish, friable, hemorrhagic soft tissue, the largest mass measuring 10 cm. in diameter. The left ovary contained a 6 cm. cyst showing similar tumor tissue. The uterus was not remarkable. The pathologic diagnosis was malignant mixed mesodermal tumor of the right ovary with metastases to the left ovary; endometriosis in both ovaries; chronic cervicitis with squamous metaplasia; and proliferative endometrium.

The patient had an uneventful postoperative course and was discharged on the thirteenth day.

In October, 1957, ascites recurred. She had numerous paracenteses, and was treated with transabdominal thioTEPA beginning on October 16. She was admitted to Garfield Memorial Hospital on Nov. 16, 1957. The abdomen was markedly distended and there was shifting dullness with a fluid wave. An x-ray diagnosis of intestinal obstruction secondary to recurrent tumor was made on Nov. 18, 1957.

Laboratory data were: hemoglobin 8.6 Gm., hematocrit 32 per cent, and leukocyte count 3,200.

Paracenteses were continued, but bilateral pleural effusion developed and she died on Dec. 11, 1957, 6 months after her first symptoms.

TABLE II. SUMMARY OF CLINICAL DATA

CASE	AGE AT DIAGNOSIS (YEARS)	POST MENOPAUSE	PRIMARY SITE	OPERATION	ADDITIONAL TREATMENT	RESULT	AUTOPSY
1	33	No	Cervix	Wertheim hysterectomy Sept. 24, 1948; left iliac and inguinal node dissection, Jan. 20, 1949; right inguinal node dissection, Jan. 27, 1949	Preoperative transvaginal irradiation, 6,400 r	Living and well, 9 years, 7 months	
2	45	No	Right ovary	Total hysterectomy, bilateral salpingo-oophorectomy, Aug. 1, 1957	Postoperative thioTEPA transabdominally and intrapleurally	Died 6 months after onset of symptoms	Metastases in mesentery, omentum, serosa of intestines, lateral pelvic walls, common iliac nodes. Intestinal obstruction secondary to metastatic tumor. Ascites. Pleural effusion
3	55	Yes	Fundus	Total hysterectomy, right salpingo-oophorectomy, left salpingectomy, May 5, 1949 (left oophorectomy 20 years prior to admission)	Preoperative intravaginal irradiation, 10,400 r; external pelvic irradiation 12,000 r	Died 11 months after treatment was begun	Recurrent tumor in pelvis. No distant metastases
4	46	Yes	Fundus	Bilateral salpingo-oophorectomy Nov. 23, 1947 (tumor considered inoperable)	Postoperative intracavitary radium, 2,800 mg. hr.; external pelvic irradiation, 7,500 r	Died 6 months after diagnosis	None performed
5	36	No	Fundus	Total hysterectomy, Jan. 24, 1941. Cecostomy for obstruction due to recurrent tumor, Oct. 31, 1941	Postoperative external pelvic irradiation, 2,000 r	Died 10 months after hysterectomy	None performed
6	47	Yes	Fundus	Cervical biopsy, Nov. 18, 1941	Radium treatment for vaginal bleeding 6 years prior to admission. Post biopsy: intravaginal irradiation, 8,000 r; external pelvic irradiation, 3,200 r; intrauterine radium, 4,800 mg. hr.	Died 15 months after diagnosis	None performed

7	55	Yes	Fundus	Total hysterectomy, bilateral salpingo-oophorectomy, October, 1952	None	Died 11 months after operation	Metastases in liver, lungs, hilar nodes, right ureter, urinary bladder. Chronic pyelonephritis. Bilateral hydronephrosis. Pulmonary edema. Bronchopneumonia
8	46	Yes	Fundus	Total hysterectomy, bilateral salpingo-oophorectomy, December, 1951	Postoperative external pelvic irradiation, 3,000 r, August, 1954; repeated external pelvic irradiation, March, 1955; irradiation of lung metastases, thioTEPA intravaginally	Died 3 years, 6 months after hysterectomy	Metastases in pelvis, lungs. Pulmonary edema
9	65	Yes	Fundus	Diagnosed at exploratory laparotomy, October, 1954	Postoperative thioTEPA intraperitoneally, intrapleurally and to scalp metastases	Died 1½ years after diagnosis	Tumor in uterus with metastases to brain, skull, lungs, liver, kidney. Pulmonary edema, bilateral pleural effusion, and ascites
10	62	Yes	Fundus	Total hysterectomy, bilateral salpingo-oophorectomy, November, 1955	Postoperative thioTEPA intrapleurally, intravenously, right sacroiliac area, March, 1956; irradiation to anterior and posterior mediastinum, 1,650 r	Died 6 months after operation	Metastases in plevis and lungs. Recent myocardial infarction, infarction of spleen and kidney
11	64	Yes	Fundus	Total hysterectomy, bilateral salpingo-oophorectomy, partial large and small bowel resection, March 19, 1957	Postoperative thioTEPA intraperitoneally, July 1, 1957, intravaginal radium	Died 3½ months after operation	Metastases in pelvic and abdominal walls, periaortic and common iliac nodes, bone marrow. Bilateral hydronephrosis and hydroureter due to ureteral obstruction by tumor. Focal pulmonary infarction, infarction of left kidney, ascites, bilateral pleural effusion

TABLE III. GROSS DESCRIPTION OF TUMORS AND LOCATION OF METASTASES AT AUTOPSY

CASE NO.	GROSS	AUTOPSY FINDINGS OR PRESENT CONDITION OF PATIENT
1	Necrotic, yellowish-gray, fungating tumor of cervix	Patient living and well
2	Yellow, hemorrhagic, soft, friable tumor of ovary	Metastases to mesentery, omentum, intestines, pelvic wall, common iliac nodes
3	Dark reddish-gray, pedunculated, whorled tumor of uterus	Recurrent pelvic tumor
4	Polypoid, rubbery, grayish-pink, gelatinous tumor of uterus, involving bladder, anterior parietal peritoneum	No autopsy
5	Polypoid, rubbery, grayish-white tumor of uterus, involving sigmoid	No autopsy
6	Firm, fungating reddish-gray tumor of uterus, cervix. Lung metastases on x-ray	No autopsy
7	Polypoid, soft, yellowish-gray tumor of fundus	Metastases to pelvic wall, bladder, lungs, liver
8	Firm, grayish-yellow tumor of fundus	Metastases to pelvic wall, lungs
9	Firm, grayish-pink tumor of fundus	Metastases to brain, skull, lungs, liver, kidney, vagina
10	Polypoid, soft, yellowish-brown tumor of fundus	Metastases to pelvic walls, lungs
11	Firm, reddish-tan tumor of uterus, right ovary	Metastases to pelvic and abdominal walls, common iliac nodes, bone marrow

TABLE IV. REPORTED FIVE-YEAR SURVIVALS

AUTHOR AND REFERENCE	YEAR REPORTED	TUMOR	SURVIVAL
von Franqué[35]	1898	Mixed sarcoma of uterus	5 years
Hartfall[12]	1931	Mixed-cell sarcoma of uterus	5 years
Perry[29]	1948	Mixed mesodermal tumor of uterus	13 years
		Carcinosarcoma of uterus	5 years
Ahumada[2]	1951	Carcinosarcoma of cervix	5 years
		Carcinosarcoma of uterus	7 years
Chesky[7]	1952	Mixed tumor of uterus	9 years
Boschann[4]	1954	Carcinosarcoma of uterus	10 years
Ulfelder[34]	1947	Sarcoma botryoides of vagina	5 years
Sternberg[31]	1954		
Symmonds and Dockerty[32]	1955	Mixed mesodermal tumor of uterus	9, 15, 18, and 19 years
Symmonds and Dockerty[33]	1955	Carcinosarcoma of uterus	9.5 years
Karpas[18]	1957	Carcinosarcoma of uterus	11 years

Autopsy findings included metastatic tumor in the mesentery, omentum, serosa of the intestines, lateral pelvic walls, and common iliac nodes. An irregular tumor nodule measuring 12 by 10 by 5 cm. filled the pelvis, and there were partial intestinal obstructions secondary to metastatic tumor in the left upper and right lower abdominal quadrants. A cut section through the tumor revealed soft, rubbery, grayish-yellow, fish-flesh tissue with soft, gray, necrotic areas of hemorrhage.

Microscopic description: Fig. 4 is a section of the tumor of the right ovary removed at operation Aug. 1, 1957, and shows a nest of epithelial cells, with varying sized nuclei

and numerous mitoses, surrounded by sarcoma, with giant cells, many bizarre cells, and spindle cells with blunt, hyperchromatic nuclei. Fig. 5 is a section taken at autopsy from a metastatic nodule, and shows a typical sarcoma pattern. Numerous sections of tumor obtained at autopsy failed to show epithelial elements in metastases.

Microscopic diagnosis: Mixed mesodermal tumor.

Comment

Case 1 is one of a small number of 5 year survivals of mixed mesodermal tumors. There has been only one previously reported patient with mixed mesodermal tumor of the cervix who survived 5 years.[2] The tumor was diagnosed when the patient was 33 years of age, and clinically appeared to be a Stage II cervical carcinoma. Irradiation did not appreciably change the tumor. Radical surgery was performed since previous experience with these tumors indicated that operation offered the best chance for the patient's survival. Because positive nodes were found at the initial operation, the two later extensive node dissections were done. Despite the pathologic reports of one positive node from each dissection, she has had no recurrence to the present time. Perhaps this shows the value of a persistent aggressive surgical attack in the therapy of these lesions.

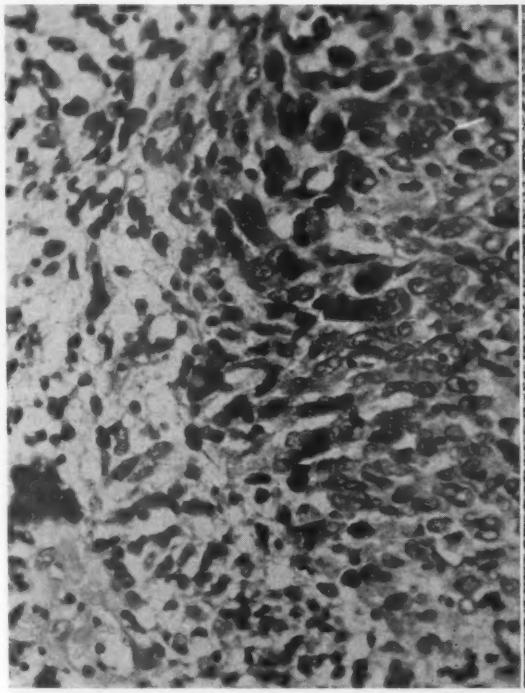


Fig. 4.

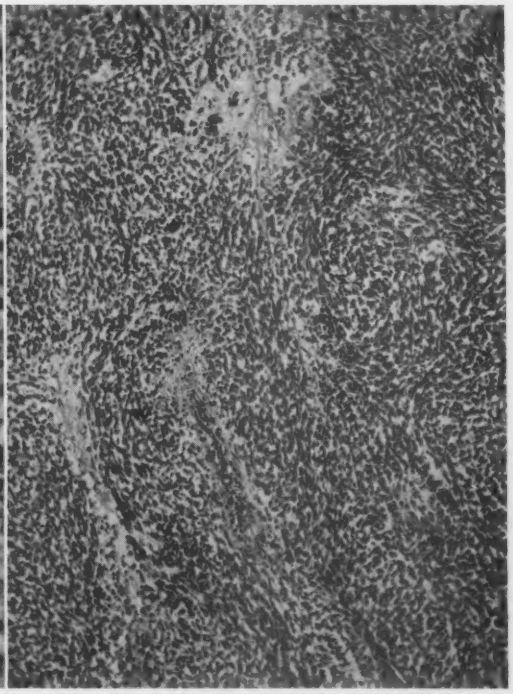


Fig. 5.

Fig. 4.—Case 2. From right ovarian tumor removed at operation. Section shows sarcoma pattern surrounding nest of epithelium-like cells. (Hematoxylin and eosin. ×300; reduced ¼.)

Fig. 5.—Case 2. From metastatic nodule at time of autopsy. Sections showed sarcoma pattern, variable in different areas, but no epithelial element. (Hematoxylin and eosin. ×100; reduced ¼.)

Case 2 arose in the right ovary in the presence of endometriosis. Grossly and microscopically the uterus was negative. Grossly a tumor appeared at the base of an ovarian cyst. Microscopically there were areas of endometriosis adjacent to areas of tumor and there was no evidence that the tumor arose

elsewhere, but no single section was present which showed the tumor arising in an endometrial cyst. This case meets Sampson's[30] criteria, listed in an article written in 1925, which are considered essential for proof that ovarian carcinoma arose in endometriosis. They are: (a) actual cancer and benign endometrial tissue must be demonstrated in the same ovary; (b) the cancer and benign endometrial tissue must bear the same relation to each other that cancer of the body of the uterus bears to the nonmalignant portions of the endometrium; (c) it must be shown that the cancer arose in this tissue and that it is not invading it from some other source. MacFarlane and Pritchard[21] reported a case in which the uterus contained leiomyomas and in which there was gross and microscopic evidence of pelvic endometriosis. There was a discoid mass attached by a stalk to the lining of an endometrial cyst in the ovary, which microscopically showed carcinosarcoma.

In one series of 889 microscopically proved cases of ovarian endometriosis, associated ovarian neoplasms were found in 7.9 per cent of the cases.[8] Six were malignant neoplasms, which represented 1.7 per cent of the series. Of these, 3 cases, or 0.9 per cent were believed to have definitely arisen in an endometrial cyst. These were a serous cystadenocarcinoma, an adenocarcinoma, and an adenoacanthoma.

Summary

Eleven cases of mixed mesodermal tumor of the female genital tract were presented, with a review of the recent literature. Two cases of special interest were presented in detail; Case 1 because it is one of a relatively few reported 5 year survivals, and Case 2 because of the origin of this tumor in the ovary.

Gratitude is expressed to Dr. Leland S. Madden for contributing Case 2, and to the Armed Forces Institute of Pathology for its assistance in photomicrography (Case 1, A.F.I.P. No. 844991, Case 2, A.F.I.P. No. 844992), and to the Pathology and Radiology Departments of Garfield Memorial Hospital, for their invaluable assistance.

References

1. Ahumada, J. C., and Arrighi, L. A.: Semana méd. **103**: 685, 1953.
2. Ahumada, J. C., Sammartino, R., and Arrighi, L. A.: Obst. y ginec. latino-am. **9**: 131, 1951.
3. Altmann, V., and Rosenthal, J.: New York J. Med. **52**: 1053, 1952.
4. Boschann, H. W.: Geburtsh. u. Frauenh. **14**: 846, 1954.
5. Bruntsch, K. H.: Zentralbl. Gynäk. **74**: 97, 1952.
6. Cantor, H.: Virginia M. Monthly **83**: 48, 1956.
7. Chesky, V. E., Dreese, W. C., and Hellwig, C. A.: Am. J. Surg. **84**: 721, 1952.
8. Corner, G. W., Hu, C.-Y., and Hertig, A. T.: Am. J. Obst. & Gynec. **59**: 760, 1950.
9. Feller, A.: Wien. klin. Wchnschr. **65**: 770, 1953.
10. Hall, J. E., and Nelms, W. F.: Am. J. Obst. & Gynec. **65**: 433, 1953.
11. Hardy, J. A., Jr., and Moragues, V.: Am. J. Obst. & Gynec. **63**: 307, 1952.
12. Hartfall, S. J.: J. Obst. & Gynaec. Brit. Emp. **38**: 593, 1931.
13. Hertig, A. T., and Sommers, S. C.: Cancer **2**: 946, 1949.
14. Hill, R. P., and Miller, F. N., Jr.: Cancer **4**: 803, 1951.
15. Hofstätter, R.: Wien. med. Wchnschr. **103**: 649, 1953.
16. Hofstätter, R.: Ztschr. Geburtsh. u. Gynäk. **141**: 45, 1954.
17. Skandalakis, J. E., Wood, M., Jernigan, S. H., and Pendergrast, W. J.: J. M. A. Georgia **46**: 200, 1957.
18. Karpas, C. M., and Speer, F. D.: A. M. A. Arch. Path. **63**: 17, 1957.
19. Klein, J.: Am. J. Obst. & Gynec. **65**: 1212, 1953.
20. Lisa, J. R., Pack, G. T., and Gioia, J.: Am. J. Obst. & Gynec. **63**: 1162, 1952.
21. MacFarlane, K. T., and Pritchard, J. E.: Am. J. Obst. & Gynec. **68**: 652, 1954.
22. Martin, J. F., Cabanne, F., and Fournie, R.: Ann. d'anat. path. **1**: 428, 1956.
23. Masubuchi, K., Tenjin, Y., and Suzuki, T.: Gann **47**: 723, 1956.
24. McCutcheon, W. B., McDonald, J. J., and Piver, J. D.: North Carolina M. J. **14**: 116, 1953.

25. McLetchie, N. G. B., and Reynolds, D. P.: Am. J. Obst. & Gynec. **65**: 1123, 1953.
26. Mossetti, C.: Minerva ginec. **5**: 316, 1953.
27. Opocher, M.: Riv. d'ostet. e ginec. prat. **34**: 161, 1952.
28. Perovic, D.: Med. Glasn. **10**: 375, 1956.
29. Perry, T., Jr.: New England J. Med. **238**: 793, 1948.
30. Sampson, J. A.: Am. J. Obst. & Gynec. **9**: 111, 1925.
31. Sternberg, W. H., Clark, W. H., and Smith, R. C.: Cancer **7**: 704, 1954.
32. Symmonds, R. E., and Dockerty, M. B.: Surg. Gynec. & Obst. **100**: 232, 1955.
33. Symmonds, R. E., and Dockerty, M. B.: Surg. Gynec. & Obst. **100**: 322, 1955.
34. Ulfelder, H., and Quan, S. H.: S. Clin. North America **27**: 1240, 1947.
35. von Franqué, O.: Münschen. med. Wehnschr. **45**: 1301, 1898.
36. Wilson, L. A., Jr., Graham, L., Thornton, W. N., Jr., and Nokes, J. M.: Am. J. Obst. & Gynec. **66**: 718, 1953.
37. Winter, G.: Zentralbl. Gynäk. **74**: 739, 1952.
38. Witt, H. J.: Geburtsh. und Frauenh. **17**: 264, 1957.

SARCOMA OF THE UTERUS

A Report of 34 Cases

E. J. Crawford, Jr., M.D., and Robert Tucker, M.D.,
Shreveport, La.

(From the Confederate Memorial Medical Center and the Highland Clinic)

SARCOMA of the uterus is a highly malignant tumor of mesodermal origin. It is an uncommon tumor and the personal experience of any one individual with this serious disease is necessarily limited. This study was undertaken to correlate the clinical findings, diagnoses, management, and ultimate outcome of each particular group of uterine sarcomas at the Confederate Memorial Medical Center and the Highland Hospital.

Material

This is an analysis of the cases seen at the Confederate Memorial Medical Center, and the Highland Hospital during the years 1948 to 1956 (9 years). The Confederate Memorial Medical Center is a Charity Hospital and a referral center for a large area of North Louisiana. The Highland Hospital is a private institute serving the city of Shreveport and adjacent area.

In this series there were 34 cases (29 from the Confederate Memorial Medical Center and 5 from the Highland Hospital). In all cases the diagnosis was confirmed by histological examination.

Frequency.—In the 9 years covered by the study there were 34 instances of sarcoma and 1,267 other malignant tumors of the uterus. This, as shown in Table I, is 2.6 per cent of all uterine malignancies. Fenton[1] reports 5.5 per cent; MacFariane,[4] 2.5 per cent; Novak,[6] 4.5 per cent; and Webb,[11] 1.8 per cent.

Table I. Frequency of Sarcoma in Uterine Malignancies, 1948-1956

	NO. CASES
Carcinoma of the cervix	1,152
Carcinoma of the endometrium	115
Sarcoma of the uterus (cervix and corpus)	34 (2.6%)
Total	1,301

Classification.—These cases are divided into three groups: leiomyosarcoma, primary (arising in the myometrium) and secondary (arising in a myoma); endometrial stromal-cell sarcoma; and mixed mesodermal tumors.

In Table II it can be seen that leiomyosarcoma makes up 76.5 per cent of our cases.

An attempt was made to divide the leiomyosarcomas into primary and secondary; however, as other writers[6, 7, 10, 11] have pointed out, it is sometimes impossible. In this series, as in all others, the secondary far out number the primary.

TABLE II. FREQUENCY OF TYPES OF SARCOMA

TYPE		NO.	%
Leiomyosarcoma		26	76.5
Primary	6		
Secondary	20		
Endometrial stromal-cell		3	8.8
Mixed mesodermal		5	14.7
Corpus	2		
Cervix	3		
Total		34	100.0

Parity.—The average parity for this series was 4.4. Fenton[1] reported the average parity to be 3. We concur with other writers[2, 11] that the nonparous woman is as likely to have sarcoma of the uterus as is the parous.

Age.—The ages of the patients with the different types of sarcoma can be seen in Table III. The average age of patients with leiomyosarcoma was 49.5 years; for the endometrial stromal, 69 years; and for the mixed mesodermal tumors, 67.4 years. There were no mixed mesodermal tumors in young girls and infants in our series. The average age for the entire series was 47.2 years. Finn[2] reported 56 years; Herman,[3] 49 years; MacFarlane,[4] 50.94; Novak,[6] the fifth decade; and Thornton,[10] 54 years.

TABLE III. AGE OF PATIENT AND TYPE OF TUMOR

TYPE	AGE (YEARS)				
	30-39	40-49	50-59	60-69	70-79
Leiomyosarcoma	6	9	4	6	1
Endometrial stromal			1		2
Mixed mesodermal					
Corpus				2	
Cervix				1	2
Total	6	9	5	9	5

Symptomatology.—Most of our patients presented one or more of the following symptoms: irregular bleeding in 25 (73.5 per cent), 15 (44.1 per cent) of whom were postmenopausal; an enlarging abdomen or abdominal mass in 8 (23.5 per cent), and lower abdominal pain in 10 (29.4 per cent). Other less frequent complaints were weight loss, weakness, and fever. The great majority of these patients had the triad of irregular bleeding, abdominal mass, and lower abdominal pain. These symptoms are not characteristic and are similar to those of other benign and malignant diseases of the uterus.

In the patients with irregular bleeding 85.7 per cent had had symptoms less than one year and 71.4 per cent had had symptoms less than 6 months.

All the patients with endometrial stromal-cell tumors complained of vaginal bleeding. Four of the 5 patients with mixed mesodermal tumors had had vaginal bleeding. This symptom was less frequent with the leiomyosarcomas as can be seen in Table IV.

TABLE IV. SYMPTOMS IN DIFFERENT TYPES OF TUMOR

TYPE	POST-MENOPAUSAL BLEEDING	MENO-METROR-RHAGIA	DISCHARGE	ENLARGING ABDOMEN OR ABDOM-INAL MASS	PAIN IN LOWER ABDOMEN
Leiomyosarcoma	8	10	2	8	10
Endometrial stromal	3				
Mixed mesodermal					
Corpus	1		2		
Cervix	3				
Total	15	10	4	8	10

Physical Examination and Diagnosis

It can be seen from Table V that the chief physical sign was enlargement of the uterus which was present in 30 cases (88.6 per cent). Two patients had tumors of the cervix and the diagnosis was made from biopsy. Two other patients had necrotic tissue in the vaginal vault from which the diagnosis was established.

Occasionally a curettage will give a positive diagnosis. In our series a diagnostic curettage was done 8 times in the patients with leiomyosarcoma; 3 were reported positive and 5 were reported negative. In the endometrial stromal type the curettement yielded a positive diagnosis in all cases. In the mixed mesodermal tumors a curettement was done in 2 cases and both were positive. One patient had a 2 cm. nodule at the umbilicus which was biopsied and reported as a mixed mesodermal tumor. In our series the only preoperative diagnoses were made from curettement or biopsy.

There are no specific physical findings of diagnostic significance in sarcoma of the uterus. In Thornton's[10] series, 7 patients had a diagnostic curettage and 3 were positive. Finn[2] used the Papanicolaou smear in 9 cases of sarcoma and 7 were positive and 2 were negative. The 2 negatives were in cases of leiomyosarcoma. Five of the positive smears were in the endometrial stromal cell type which is to be expected. It is a little surprising, however, that 2 leiomyosarcomas yielded positive smears. Our series is in accord with those of other writers in that the diagnosis of the leiomyosarcoma is usually made on histological examination of the surgical specimen.

TABLE V. SIZE OF UTERUS AND TYPE OF SARCOMA

SIZE OF UTERUS	LEIOMYOSARCOMA	STROMAL CELL	MIXED CORPUS	MESODERMAL CERVIX
Normal uterus	1			3
Uterus enlarged from pubis to umbilicus	23	3	2	
Uterus above umbilicus	2			
Total	26	3	2	3

Treatment

Leiomyosarcoma.—Three cases (11.5 per cent) were considered inoperable. Two of these had exploratory laparotomy and biopsy of the pelvic mass. In the other case the diagnosis was made from tissue lying in the vagina. This patient was treated with external irradiation and died 6 months after treatment. The irradiation did not affect the size of the mass.

Twenty-three patients were treated surgically, 16 (69.8 per cent) by total abdominal hysterectomy, 6 (26.0 per cent) by subtotal abdominal hysterectomy, and one by the vaginal approach. At operation 3 patients had pelvic extension of the disease. Two of these patients died within 13 months of operation; the other was lost to follow-up so is assumed to be dead.

In 3 cases of secondary sarcoma, external irradiation was given after operation. There was no evidence of extension at operation. Two of these patients are living and one died 13 months after treatment.

Table VI shows the follow-up of the patients treated by a total abdominal hysterectomy. The 5 year survival in the total hysterectomy group was 44 per cent. All the survivors had a sarcoma secondary to a malignant transformation of a fibromyoma. Three of the dead had a primary sarcoma; the other 4 dead had a secondary sarcoma.

TABLE VI. FOLLOW-UP AFTER TOTAL ABDOMINAL HYSTERECTOMY FOR LEIOMYOSARCOMA

Total abdominal hysterectomy	16	7 dead 1 recurrence in 7½ months 1 pulmonary metastases, 13 months 1 intestinal obstruction 17 days after operation 1 lost to follow-up, assumed to be dead 3 State Health Department notified hospital of patient's death
		9 living 1 2-3 years 1 4-5 years 3 5-6 years 1 6-7 years 3 7-8 years
5 year survival	44%	

Table VII records the follow-up in the cases treated by other methods. The 5 year survival in the subtotal hysterectomy group was 33.3 per cent (2 cases). Both survivors had a secondary sarcoma.

TABLE VII. FOLLOW-UP AFTER OTHER TYPES OF TREATMENT

Subtotal hysterectomy	6	4 dead 1 recurrence 13 months 1 recurrence 3 years 1 pulmonary metastases 2 months 1 unknown, 5 years, 8 months' survival
		2 living
5 year survival	33.3%	1 5-6 years 1 6-7 years
Vaginal hysterectomy	1	1 living, 3 years
X-ray only	1	1 dead 6 months. Intestinal obstruction secondary to extension of tumor
Exploratory laparotomy (inoperable)	2	1 living 3 months 1 dead, 1 month, 17 days. Perforation of rectum and peritonitis

The over-all 5 year survival for leiomyosarcoma in our series was 34.6 per cent (9 cases). Finn[2] reported 11 per cent; and Webb,[11] 13.6 per cent. All our survivors had a secondary sarcoma and the diagnosis was made by microscopic examination of the surgical specimen. Of the 9 survivors, only one was postmenopausal. The secondary sarcoma is the most favorable type but it is not innocuous. Only 9 of the 20 patients (45 per cent) survived 5 years.

Endometrial Stromal-Cell Sarcoma.—In our series this type of sarcoma was invariably fatal. All our patients were dead within 6 months after the diagnosis was established. A follow-up of these patients is shown in Table VIII.

There were no 5 year survivals. McDonald[5] reviewed all the slides of uterine tumors removed at the Mayo Clinic from 1904 to 1939. He found 18 endometrial sarcomas. At the end of 6 years there were only 2 patients (11.1 per cent) alive. Webb[11] reported a 5 year survival of 40 per cent. He believed this type of sarcoma to be responsive to x-ray. Finn[2] reported a 39 per cent survival.

Mixed Mesodermal Tumors.—Table IX gives the follow-up study of the patients with mixed mesodermal tumors. Sixty per cent (3 cases) had extension at the time of surgery and were deemed inoperable. Two of these were treated by external irradiation and the other one died without any treatment. All 3 died within 5 months after diagnosis.

Forty per cent (2 patients) were treated surgically. One patient died 4½ years after operation. The other one is living with a survival of 2 years. There are no 5 year survivals in our series.

TABLE VIII. FOLLOW-UP OF ENDOMETRIAL STROMAL-CELL SARCOMA

Total abdominal hysterectomy plus x-ray	1	1 dead 6 months after operation. Intestinal obstruction due to recurrence
X-ray only	1	1 dead. 6,000 r of x-ray
No treatment	1	1 dead 6 months

TABLE IX. FOLLOW-UP OF MIXED MESODERMAL TUMORS

Abdominal hysterectomy	2	1 dead 4½ years after operation 1 living 2-3 years
External x-ray	2	2 dead, both 5 months after treatment
No treatment	1	1 dead 1 month after diagnosis. Metastases to umbilicus and abdominal cavity

Sternberg[8] reviewed 21 cases of mixed mesodermal tumor at the Charity Hospital of New Orleans. The treatment was surgery, irradiation, nitrogen mustard, and various combinations of these. All their patients are now dead; the longest survivor lived only 27 months after the onset of symptoms. The average survival for their series was 8.4 months.

Webb[11] reported 3 cases of mixed mesodermal tumor; 2 of these at the time of operation had extension and were treated with x-ray after surgery. The other patient had a total hysterectomy without x-ray. The former 2 are living 12 years after operation, the latter died with pulmonary metastases 30 months after operation. The 5 year survival rate was 66.6 per cent.

Symmonds[9] reports 19 cases with 4 survivals for 5 years (21 per cent). Two had a total abdominal hysterectomy and x-ray; and the other 2 had a total abdominal hysterectomy without x-ray.

Survival Rate

The 5 year survival rate in the 34 cases of sarcoma of the uterus in this series was 26.4 per cent. Novak[6] reported 30 per cent; MacFarlane,[4] 29.6 per cent; Herman and Barrows,[3] 33 per cent.

The operative mortality for all types of sarcoma was 3.8 per cent. MacFarlane[4] reported 11.1 per cent; Finn,[2] 10 per cent; Herman and Barrows,[3] no operative mortality.

The cause of death was definitely established in 5 cases. An autopsy was done in 3 and all had recurrence in the pelvis. Two of the 3 had been operated on and extension through the serosal surface of the uterus was noted at that time. The other patient had a frozen pelvis and was deemed inoperable.

Pulmonary metastasis had been demonstrated by x-ray in 2 other patients who died. If there was pelvic extension, the disease was invariably fatal regardless of the treatment.

Summary

1. Thirty-four cases of sarcoma of the uterus which occurred in a 9 year period are presented.

2. Sarcomas constituted 2.6 per cent of all uterine malignancies.

3. Curettement established the diagnosis in 8 cases.

4. Operation is the treatment of choice.

5. The operative mortality was 3.8 per cent.

6. Irradiation is of doubtful benefit.

7. The extent of the tumor is the most important factor in prognosis. All patients in whom the sarcoma extended outside the uterus are dead.

8. Earlier diagnosis may possibly increase the survival rate.

9. The 5 year survival rate in this series was 26.5 per cent.

10. There were no 5 year survivors in the endometrial stromal-cell and mixed-mesodermal group.

11. The leiomyosarcoma arising in a fibromyoma is the most favorable type of sarcoma.

References

1. Fenton, A. N., and Burke, L.: Am. J. Obst. & Gynec. 63: 158, 1952.
2. Finn, W. F.: Am. J. Obst. & Gynec. 60: 1254, 1950.
3. Herman, L., and Barrows, D. N.: Obst. & Gynec. 6: 18, 1955.
4. MacFarlane, K. T.: Am. J. Obst. & Gynec. 59: 1304, 1950.
5. McDonald, J. R., Broders, A. C., and Counseller, V. S.: Surg. Gynec. & Obst. 70: 223, 1940.
6. Novak, E., and Anderson, D. F.: Am. J. Obst. & Gynec. 34: 740, 1937.
7. Scheffey, L. C.: S. Clin. North America 25: 1262, 1945.
8. Sternberg, W. H., Clark, W. H., and Smith, R. C.: Cancer 7: 704, 1954.
9. Symmonds, R. E., and Dockerty, M. B.: Surg. Gynec. & Obst. 100: 232, 1955.
10. Thornton, W. N., Jr., and Carter, J. P.: Am. J. Obst. & Gynec. 62: 294, 1951.
11. Webb, G. A.: Obst. & Gynec. 6: 38, 1955.

GRANULAR-CELL MYOBLASTOMA OF THE VULVA

Review of the Literature and Report of Four Cases

ALAN RUBIN, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and the Gynecean Hospital Institute for Gynecologic Research of the School of Medicine and Hospital of the University of Pennsylvania)

GRANULAR-CELL myoblastoma is a tumor which was first described in 1926 by Abrikossoff,[1] hence the eponym, Abrikossoff's tumor. It characteristically occurs as a small, solitary, painless, poorly encapsulated mass resembling a fibroma. Microscopically it is composed of irregular strands of fascicles of large, elongated cells resembling myoblasts, and containing coarse, granular, eosinophilic cytoplasm. The cells may have indistinct borders, giving the appearance of a multinucleated granular cytoplasmic mass. Varying amounts of fibrous tissue are present. When the tumors arise directly beneath squamous epithelium, as in the skin, vulva, oropharynx, or tongue, the overlying epithelium may show abnormal proliferation suggestive of early squamous-cell carcinoma.

The histogenesis of the tumor is obscure. Indeed, four principal tissues of origin have been suggested: striated muscle, histiocytes, fibroblasts, and peripheral nerves.[2] Evidence in favor of a neural origin is increasing.[2]

Only 19 cases of its occurrence in the vulva have been reported.[2-18] They are summarized in Table I. Sixteen of the reports have been published within the last 10 years. This, combined with the fact that 4 cases which have been discovered in one institution are herein reported, suggests that the tumor may not be as rare as was previously thought, and that more cases will be diagnosed as awareness of this lesion grows.

CASE 1.—E. M., a 30-year-old white para ii, during the course of examination because of intermenstrual bleeding, was discovered to have a 1 cm., firm, movable, nontender mass in the region of the left Bartholin's gland. A dilatation and curettage, biopsy of the cervix, and excision of the mass were performed. At operation it was noted that no definite cleavage plane was present between the mass and the surrounding vulvar tissues. The tumor was excised with but little surrounding tissue. The cut surface was pale gray and smooth. Microscopic sections (Fig. 1) showed it to be composed of fairly large pink-staining cells, closely packed together, with small nuclei. The cells tended to be spindle shaped in some areas, and were arranged in bundles or whorls. The cell borders were distinct in some areas, indistinct in others. The bundles of cells were separated by varying amounts of fibrous tissue. The epithelium overlying the tumor was not removed. The patient has been free of evidence of recurrence for 3 years.

CASE 2.*—A. D., a 48-year-old white woman, had noticed a slowly increasing lump in the skin of the left labium majus for 3 years. Examination showed a solid 1.5 by 1 cm. mass in the left labium majus. It appeared to lie just beneath the skin and to be attached to it. It was thought to be a calcified sebaceous cyst. The mass was excised under local anesthesia. On cut surface it was grayish brown and homogeneous. Microscopic examination showed the overlying epidermis to be normal. The tumor (Fig. 2) was composed of large cells containing coarsely granular eosinophilic cytoplasm. The supporting stroma consisted of dense,

Fig. 1.—Case 1. Note the typical large cells with coarse, granular cytoplasm, small nuclei, and frequently indistinct cell borders. (×250; reduced ¼.)

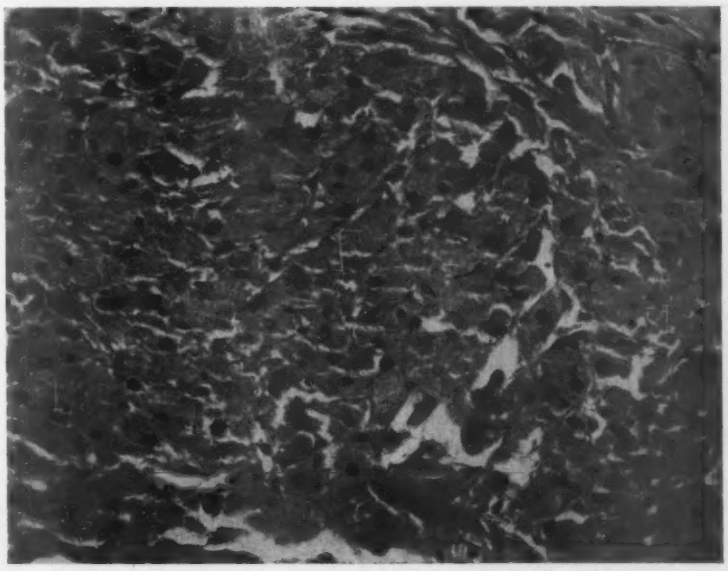


Fig. 2.—Case 2. Section illustrates the indistinct cell borders, giving the appearance of a multinucleated granular cytoplasmic mass. (×250; reduced ¼.)

*Patient of Dr. William T. Fitts, Jr., with whose kind permission this case is reported.

TABLE I. SUMMARY OF ALL REPORTED CASES OF GRANULAR-CELL MYOBLASTOMA OF THE VULVA

AUTHOR	YEAR REPORTED	AGE	RACE	DURATION OF SYMPTOMS	TUMOR SIZE (LARGEST DIAMETER IN CM.)	TREATMENT	RESULTS
1. von Szathmáry[3]	1937	32	White	Unknown	0.5	Local excision, then wide excision after recurrence	Recurrence in 3 months, then reoperation. Not stated for second operation
2. Tamis and Kowles[4]	1941	39	White	3 years	2.6	Local excision	No recurrence in 6 months
3. Powell[5]	1946	26	Negro	13 years	4.0	"Removal"	No recurrence in 1½ years
4. Murphy, Dockerty, and Broders[6]	1949	72	Negro	Unknown	3.5	Excision	Not stated
5. Kern, Kaufman, and Combes[7]	1950	25	Negro	1.5 years	4.5	Wide, deep excision	No recurrence in 3 months
6. Irgang and Ultmann[8]	1951	25	Negro	2 years	3.5	Excision	Not stated
7. Wright[9]	1951	61	White	2 years	3.0	Wide excision	No recurrence in one year
8. Bangle[2]	1952	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
9. Valentine and Thomas[10]	1953	54	Negro	2 years	2.0	Local excision	No recurrence in 3 months
10. Watson and Taylor[11]	1953	32	White	2 years	2.0	Local excision	No recurrence in one year
11. Sullivan, Malfetano, and Marsh[12]	1954	23	Negro	22 years	3.0	Excision	No recurrence in 5 months
12. Reich et al.[14]	1954	33	Negro	4 years	1.3	Local excision	No recurrence in 1½ years
13. Clarke[13]	1956	14	Not stated	6 weeks	2.8	Local excision	No recurrence in 1½ years
14. Hanson and Beecham[15]	1956	54	White	1 year	2.3	Wide excision	No recurrence in one year
15. Hanson and Beecham[15]	1956	39	Negro	6 months	2.5	Local excision, then vulvectomy	No recurrence in 6 months
16. Hanson and Beecham[15]	1956	50	Negro	6 months	2.5	Not stated	Not stated
17. Mitchell and Kaplan[16]	1956	42	White	2 years	1.5	Enucleation	No recurrence in 1½ years
18. Chiodi et al.[17]	1957	22	Negro	6 weeks	5.0	Wide excision	No recurrence in approximately one year
19. Winkelstein and Friedman[18]	1958	50	White	1.5 years	3	Local excision	Not stated
20. Rubin (this report)	1958	30	White	Unknown	1.0	Local excision	No recurrence in 3 years
21. Rubin (this report)	1958	48	White	3 years	1.5	Wide local excision	No recurrence in 8 years
22. Rubin (this report)	1958	45	Negro	1 year	0.5	Wide local excision	No recurrence in 1 year
23. Rubin (this report)	1958	37	Negro	6 years	Multiple, 0.5 to 2.0	Wide local excision	No recurrence in 6 months

collagenous connective tissue. The tumor was found to extend to the edge of the excised tissue. Accordingly, 3 weeks later a wide local excision was carried out. A small amount of residual tumor was found. The patient has remained free of evidence of recurrence for 8 years.

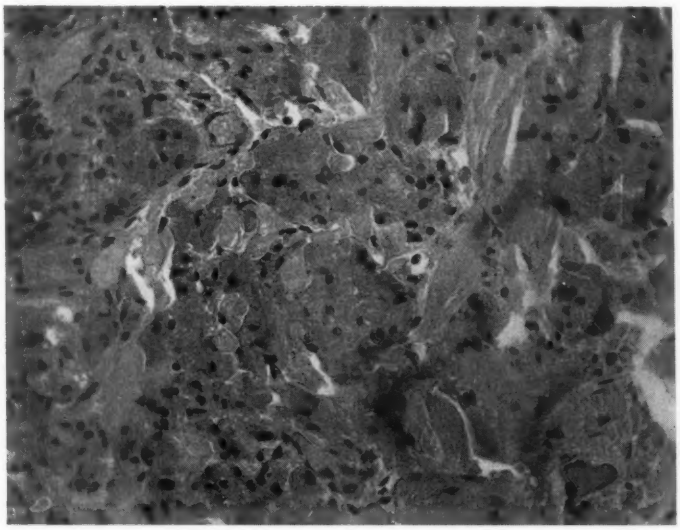


Fig. 3.—Case 3. The large, granular cells set in a dense fibrous stroma are clearly seen. (×250; reduced ¼.)

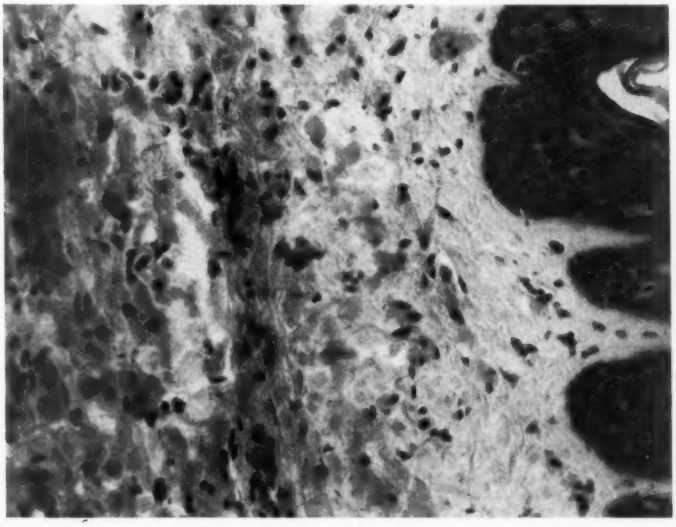


Fig. 4.—Case 4. Here there is more fibrous stroma. Note that the epithelium overlying the tumor shows some increased activity, although this is not as prominent as it sometimes is. (×250; reduced ¼.)

CASE 3.—E. A., a 45-year-old Negro para iv, had noted a 0.5 cm. mass of the right labium majus for one year. It was thought to be a sebaceous cyst and excision was performed as an outpatient procedure under local anesthesia. The lesion was found to be a solid tumor which on cut section grossly resembled a fibroma. Microscopic examination

showed the overlying skin to be normal. The tumor consisted of typical granular myoblastoma cells in a fibrous stroma (Fig. 3). It extended to the edge of the specimen. The patient was then admitted and a wide excision performed under general anesthesia. The specimen removed showed residual tumor. There has been no evidence of recurrence in one year.

CASE 4.—G. B. was a 37-year-old Negro para i. In 1949 she received x-ray and radium for a squamous-cell epithelioma of the cervix, Stage II (International). In 1952 she noted a tiny lesion described as a "pimple" on the right labium majus. It was nontender. It gradually increased over the next 6 years to the size of a 5 cent piece. Three other discrete nodules appeared, and gradually increased in size. One was excised elsewhere under local anesthesia in 1955. It is not known whether that tissue was submitted to microscopic examination. The lesion gradually reappeared. Another nodule was excised under local anesthesia in the outpatient clinic of the Hospital of the University of Pennsylvania. Microscopic examination of the tissue removed showed a typical granular-cell myoblastoma which had been incompletely removed (Fig. 4). The patient was advised to be admitted to the hospital for more complete excision of the lesions. She procrastinated for 4 months. During this time the nodule which had been excised recurred. When she finally consented to operation the four lesions were widely excised, including the overlying skin. They were firm nodules ranging in size from 2 cm. to 0.5 cm. Each was in the subcutaneous tissue, and freely movable. All on gross examination resembled fibromas. Microscopic examination of the tumors showed islands and strands of large, elongated cells containing granular pink-staining cytoplasm and small oval nuclei within the dermis. The epidermis appeared normal. There has been no recurrence in 6 months.

Comment

Granular-cell myoblastomas appear to have no particular predilection as to age or race. The clinical story is usually that of a slow-growing, firm, nonpainful nodule.

When they occur in the vulva they are usually confused with sebaceous cysts, fibromas, hidradenomas, or lesions of Bartholin's gland. If the overlying skin ulcerates, they can be misdiagnosed as basal-cell or squamous-cell carcinomas. The tumor itself, since it is not encapsulated, may be incompletely excised. Such a practice might be dangerous, since, although the great majority of these tumors are benign, they may recur if incompletely removed. Indeed, they have been reported to have metastasized in rare instances.[5]

The tumors are said to be radioresistant,[19] hence wide local excision is the treatment of choice.[15, 17]

Summary

Four cases of granular-cell myoblastoma of the vulva are added to the 19 previously reported in the literature. In 3 of the 4 the tumors were diagnosed preoperatively as sebaceous cysts and excised under local anesthesia. In each instance, microscopic examination of the tissue obtained indicated incomplete removal of the tumor. This was confirmed when the patients were reoperated upon and wider excision performed. In one patient, such inadequate excision was followed by local recurrence on two occasions. Thus, while the great majority of these tumors are benign, wide local excision is important to avoid recurrence. Very rarely, granular-cell myoblastomas have been noted to metastasize.

References

1. Abrikossoff, A.: Virchows Arch. path. **260**: 215, 1926.
2. Bangle, R., Jr.: Cancer **5**: 950, 1952.
3. von Szathmáry, Z.: Ztschr. Geburtsh. u. Gynäk. **114**: 371, 1937.
4. Tamis, A. B., and Kowles, J. J.: Am. J. Obst. & Gynec. **42**: 543, 1941.
5. Powell, E. B.: Arch. Path. **42**: 517, 1946.
6. Murphy, G. H., Dockerty, M. B., and Broders, A. C.: Am. J. Path. **25**: 1157, 1949.
7. Kern, A. B., Kaufman, J. J., and Combes, F. C.: Arch. Dermat. & Syph. **62**: 109, 1950.
8. Irgang, S., and Ultmann, R.: Harlem Hosp. Bull. **4**: 31, 1951.
9. Wright, J. L.: New Zealand M. J. **50**: 560, 1951.
10. Valentine, F. M., and Thomas, J. R.: Am. J. Obst. & Gynec. **65**: 213, 1953.
11. Watson, H. B., and Taylor, C. W.: J. Obst. & Gynaec. Brit. Emp. **60**: 917, 1953.
12. Sullivan, T. F., Malfetano, J., and Marsh, M. R.: Am. J. Obst. & Gynec. **67**: 687, 1954.
13. Clarke, J. Y.: Personal communication to Hanson and Beecham.[15]
14. Reich, W. J., Doswald, A. M., Williams, P. C., and Nechtow, M. J.: J. A. M. A. **156**: 714, 1954.
15. Hanson, S. M., and Beecham, C. T.: Am. J. Obst. & Gynec. **71**: 190, 1956.
16. Mitchell, J. A., and Kaplan, D.: Am. J. Obst. & Gynec. **71**: 901, 1956.
17. Chiodi, N. E., Siegel, I. A., Guerin, P. F., and McCaughan, D.: Obst. & Gynec. **9**: 472, 1957.
18. Winkelstein, L. B., and Friedman, S.: Am. J. Obst. & Gynec. **75**: 325, 1958.
19. Horn, R. C., Jr., and Stout, A. P.: Surg. Gynec. & Obst. **76**: 315, 1943.

GLYCOGEN CONTENT OF THE EPIDERMIS OF THE VULVA IN THE PRESENCE OF LEUKOPLAKIA AND OF SQUAMOUS-CELL CARCINOMA

Histochemical Study of 98 Specimens

DAVID I. SEIBEL, M.D., MINNEAPOLIS, MINN.

(From the Department of Obstetrics and Gynecology, University of Minnesota Medical School)

DURING the performance of a battery of histochemical tests on specimens of normal, leukoplakic, and carcinomatous vulvar skin, large quantities of glycogen were found in the stratified squamous epithelium in cases of leukoplakia. This observation was pursued. The following report is based on the histologic study of biopsy and operative specimens from 98 patients.

Methods

Tissue to be stained was fixed for approximately 12 hours in ten per cent formalin, and embedded in paraffin. Paraffin blocks stored in the pathology laboratory for as long as 5 years were found to be still usable for the demonstration of glycogen. Lillie[1] stated that cell glycogen is loosely bound to protein and is preserved with protein fixatives. It is to be noted, however, that glycogen is apparently dissolved out of specimens stored for any length of time in formalin solution.

Three slides were made from each block. One was stained with hematoxylin and eosin. The second was stained for glycogen by the Hotchkiss-McManus technique.[2, 3] The latter involves the oxidation of adjacent hydroxyl groups to aldehydes by means of periodate, and the coloring of the aldehydes with Feulgen reagent (leukofuchsin). Polysaccharides are indicated by a violet fuchsin color. The differentiation of glycogen from other substances that give a positive reaction was made by the use of saliva on the third slide to selectively digest away the glycogen prior to staining. Authorities in the field of histochemistry agree that the method used herein is a valid one for the demonstration of glycogen.[4, 5, 6]

Observations

Normal Vulva (30 Patients).—The vestibular epithelium, like the vaginal mucosa, contains considerable quantities of glycogen at all ages. There is no histochemically demonstrable decrease in the concentration of glycogen in the mucous membrane of the vagina or vestibule after the menopause. Fig. 1 is a biopsy specimen of the vestibular wall of a woman 66 years of age, demonstrating the typical glycogen deposition in the stratified squamous epithelium. The stratum germinativum contains no glycogen. The stratum spinosum is composed of approximately 20 layers of cells. The periphery of and the interstices between these cells are heavily laden with glycogen, giving this stratum a tilelike pattern.

The labia minora contain little or no glycogen. Fig. 2 is a biopsy specimen of normal labium minus stained for glycogen. The epithelium is devoid of histochemically demonstrable carbohydrate.

Fig. 3 is a biopsy specimen of normal labium majus stained for glycogen. Here, too, the epithelium is free of demonstrable glycogen. The outer-root sheath of the hair follicle, however, contains considerable glycogen. In this regard, the labium majus has the same characteristics as external skin elsewhere.[7]

Leukoplakia (38) Patients.—Large quantities of glycogen were found in the stratified squamous epithelium of 32 of the 38 specimens of vulvar leukoplakia. The deposition of the glycogen is not as uniform in appearance as it is in the epithelium of the vestibule, and its distribution is different. In leukoplakia, the cytoplasm of the cells of the stratum spinosum takes up the fuchsin stain diffusely, with additional coarse purple granules of various sizes dispersed within the cytoplasm. The glycogen-stained cytoplasm forms a halo about the unstained cell nucleus. The cell interstices stand out sharply in relief, as they too are unstained. As usual, the stratum germinativum is free of glycogen. The concentration of glycogen within the leukoplakic epithelium may vary considerably from one microscopic field to the next, intensely stained areas and areas with trace amounts lying side by side.

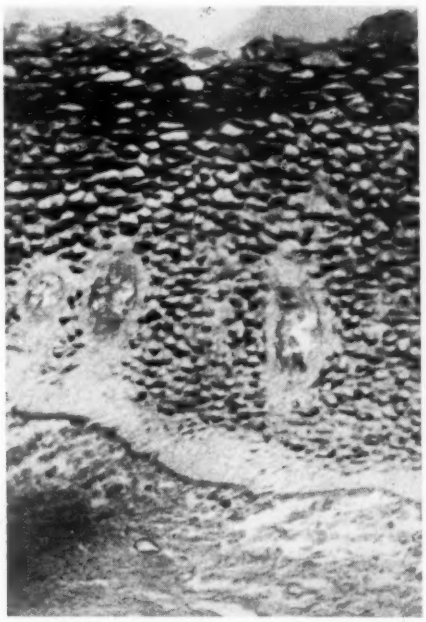


Fig. 1.—Biopsy specimen of vestibular wall. Glycogen is deposited at the periphery of the cells of the stratum spinosum. (Glycogen stain. ×186; reduced ⅙.)

Fig. 4 is an example of the glycogen deposition in leukoplakic epithelium.

Fig. 5 demonstrates the lack of uniformity in the concentration of stainable glycogen in adjacent areas of leukoplakia.

Fig. 6 demonstrates the interesting finding of mycelia within the cornified layers of a leukoplakic epithelium. Yeastlike structures on the surface of leukoplakia were found in two other biopsy specimens in this series.

Leukoplakia-Carcinoma Complex (30 Patients).—Adjacent areas of leukoplakia and squamous-cell carcinoma of the vulva are seen in Figs. 7 and 8. The

spinous cells of the leukoplakic epithelium are rich in glycogen. The nests of tumor cells are free of histochemically demonstrable glycogen. These findings were uniformly present in this group of specimens.

Occasionally, in areas of carcinoma where the basal cells are undergoing differentiation and pearl formation, glycogen appears in the spinous cells of the tumor. The pearls also take up the fuchsin stain, but the purple color resists treatment with saliva. Epithelial pearls, then, contain polysaccharide material which is not glycogen.

A frequent observation is presented in Fig. 9. The orderly epithelium on the surface of a carcinoma is found to contain glycogen similar to that in leukoplakic areas, while the carcinomatous pegs at depth remain unstained.

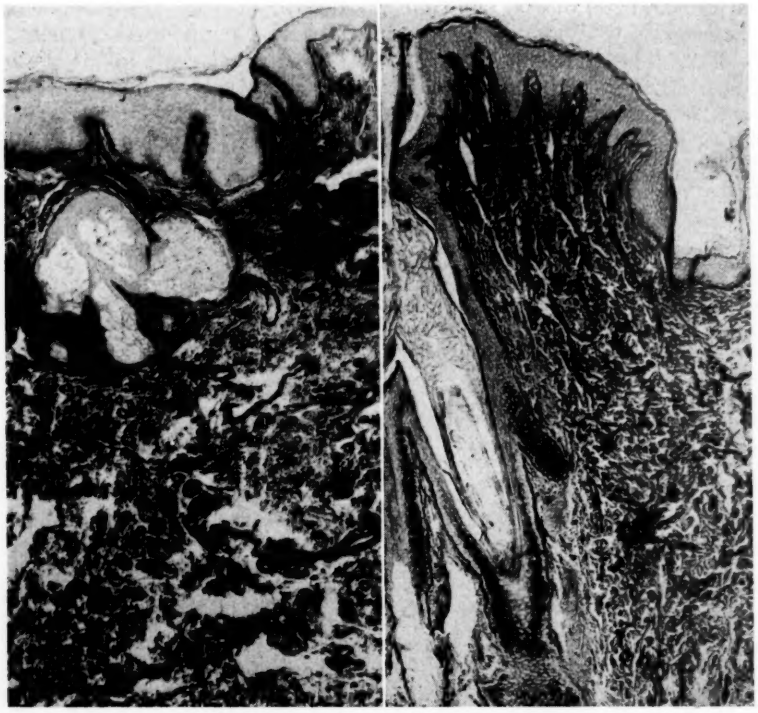


Fig. 2. Fig 3.

Fig. 2.—Biopsy specimen of normal labium minus. There is no demonstrable glycogen in the epithelium. (Glycogen stain. ×70; reduced 1/6.)

Fig. 3.—Biopsy specimen of normal labium majus. Glycogen is present in the root of the hair follicle. The shading of the surface epithelium is artifact. (Glycogen stain. ×70; reduced 1/6.)

Comment

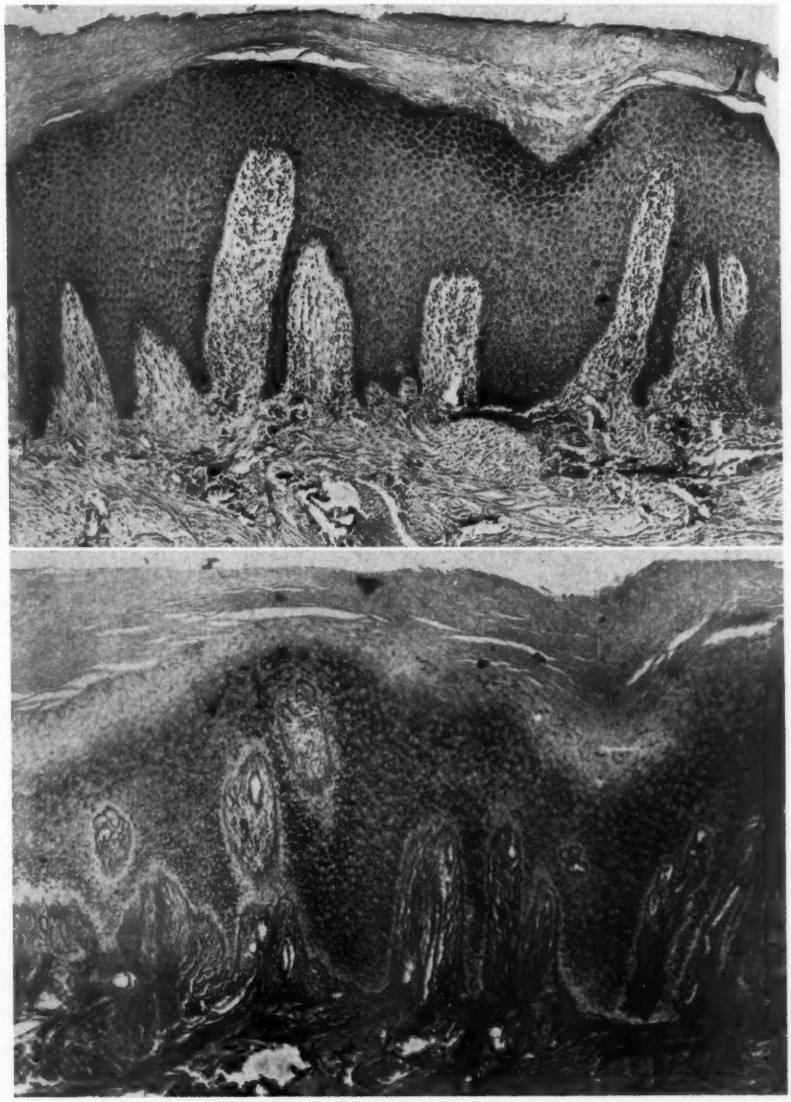
In human epidermis, the stratum spinosum contains little or no histochemically demonstrable glycogen. Only the outer-root sheath of hair follicles contains glycogen in considerable amounts.[7]

The stratified squamous epithelium of the labia majora and minora, like skin elsewhere, normally contains little or no histochemically demonstrable glycogen. The epithelium of the vestibule behaves like the vaginal mucosa.

In leukoplakia of the vulva, large quantities of glycogen are demonstrable in the stratum spinosum. This glycogen is stored mainly within the cytoplasm,

in contradistinction to the vagina, where the glycogen is deposited mainly along cell boundaries. In leukoplakia, glycogen deposition within the epithelium and excessive keratinization appear to be related. This is in accord with the theory that the anaerobic glycolysis of glycogen in proliferating stratified squamous epithelium is the source of energy for keratin protein synthesis.[8] This theory further explains the absence of glycogen in the stratum germinativum on the supposition that basal cells are adequately nourished by the dermal capillaries.

A.



B.

Fig. 4.—Biopsy specimen of leukoplakia of the vulva. Large quantities of glycogen are deposited within the cytoplasm of the cells of the stratum spinosum. *A*, Hematoxylin and eosin stain. *B*, Glycogen stain. (×70; reduced ⅙.)

The finding of yeastlike organisms on the surface of leukoplakic skin in three biopsy specimens in this series is interesting. Rothman[9] believes that an increase in the amount of glucose in the skin surface film might promote the infection and further growth of *Candida albicans* in the horny layer. Growth of mycelia may be one cause of the pruritus frequently associated with leukoplakia.

The undifferentiated basal cells of squamous-cell carcinoma of the vulva are free of histochemically demonstrable glycogen. It is not surprising that glycogen should appear in the spinous cells of a tumor undergoing differentiation,

Fig. 5.

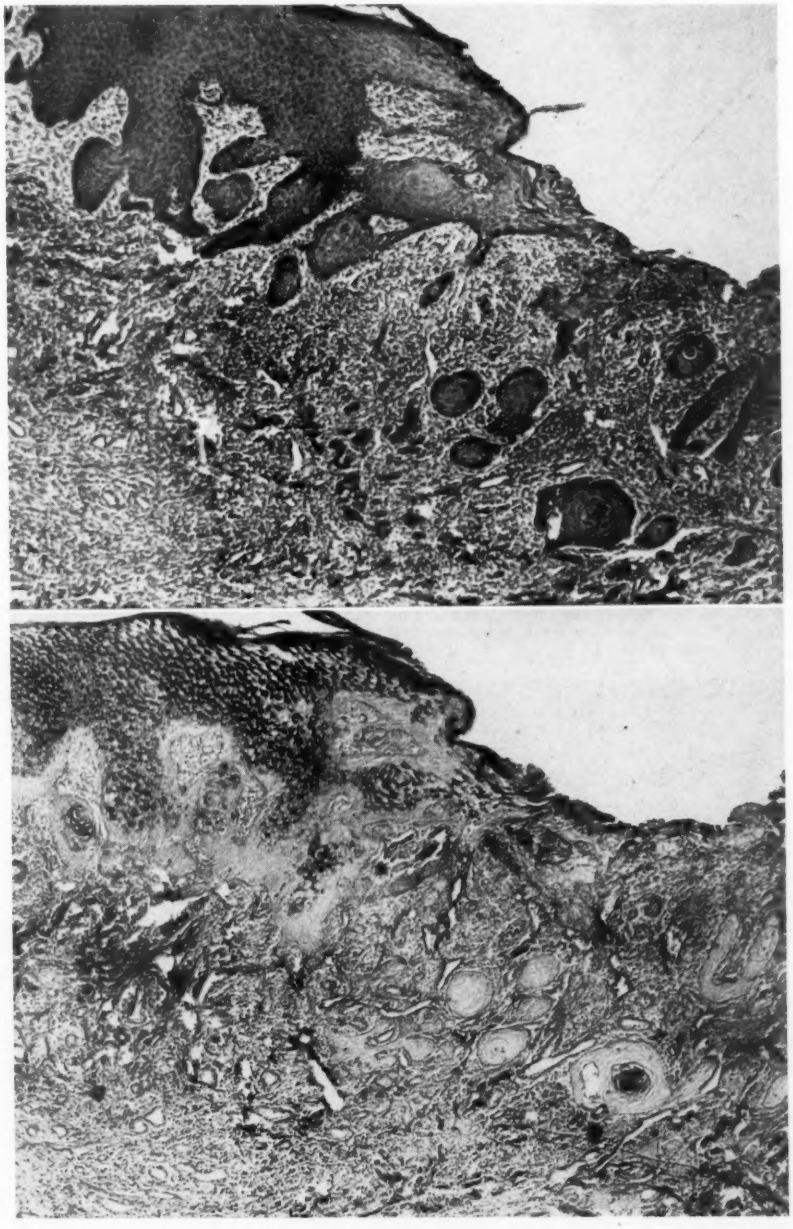
Fig. 6.

Fig. 5.—Photomicrograph demonstrating the lack of uniformity in the concentration of glycogen in leukoplakic epithelium. (Glycogen stain. ×70; reduced ⅙.)

Fig. 6.—Photomicrograph demonstrating mycelia in leukoplakic epithelium. (Glycogen stain. ×410; reduced ⅙.)

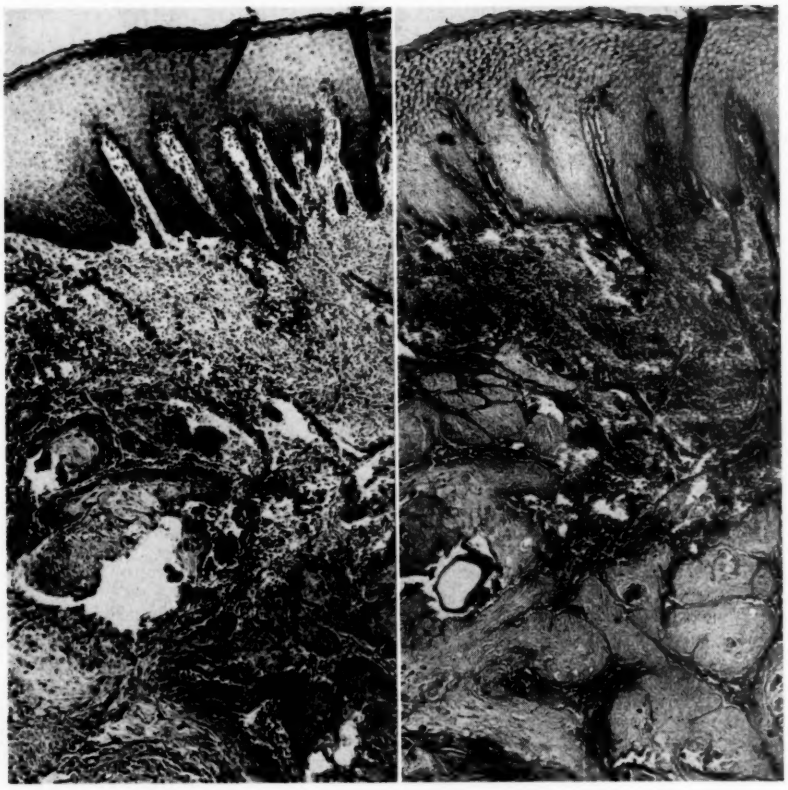
as this occurs in the leukoplakic forerunner. Glycogen has been found in squamous-cell carcinoma of skin elsewhere, with the use of Best's carmine technique.[10]

A.



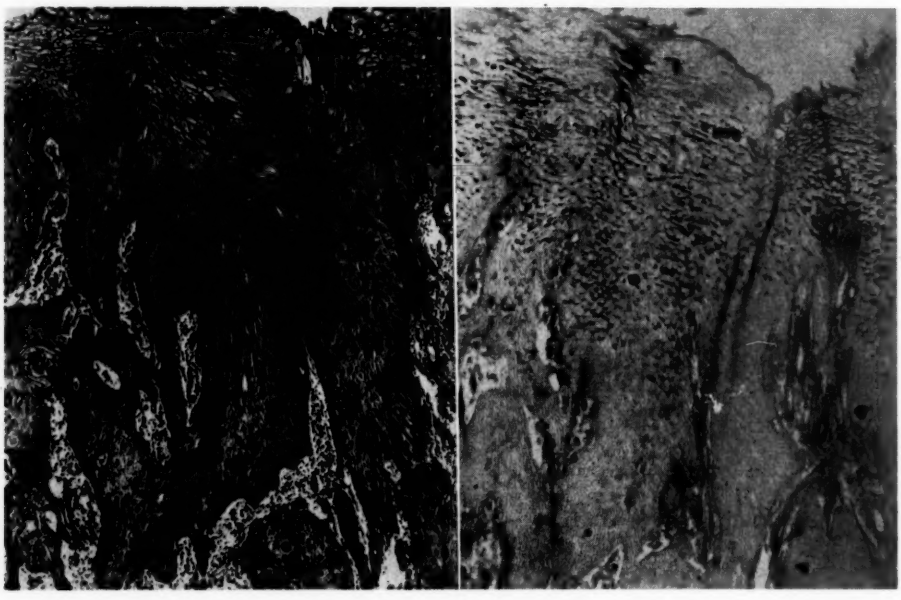
B.

Fig. 7.—Biopsy of leukoplakia-carcinoma complex. In *B*, the leukoplakic epithelium on the left is rich in glycogen, while the nests of tumor cells to the right are free of glycogen. *A*, Hematoxylin and eosin stain. *B*, Glycogen stain. (×70; reduced 1/6.)



A. *B.*

Fig. 8.—Biopsy specimen of leukoplakia-carcinoma complex. The tumor cells below the leukoplakic epithelium are free of glycogen. *A*, Hematoxylin and eosin stain. *B*, Glycogen stain. (×70; reduced ⅙.)



A. *B.*

Fig. 9.—Biopsy specimen of carcinoma of the vulva. Only the more superficial portions of the epithelium contain glycogen. *A*, Hematoxylin and eosin stain. *B*, Glycogen stain. (×70; reduced ⅙.)

It is unfortunate that the glycogen distribution in leukoplakia is often spotty in nature, even in adjoining areas on the same slide. In the light of what is known at present, this would make the use of glycogen staining as a means of diagnosing early carcinoma unreliable. A glycogen-free area within a leukoplakia specimen is not necessarily malignant. The observation that surface levels of carcinoma of the vulva arising in leukoplakia often contain glycogen, while lower layers of full-blown carcinoma do not, may indicate that carcinoma of the vulva grows slowly by extension from basal cells, but takes a long time to destroy the leukoplakic skin at the surface.

The observations reported in this paper suggest that glycogen storage in the spinous cells of leukoplakia is a fundamental metabolic process of this proliferative vulvar lesion. The glycogen deposition may be a compensatory reaction to local tissue anoxia.[11] Glycogen is a source of energy for keratin synthesis. Furthermore, carbohydrates have been shown to be mitogenic for skin.[12] The consequences of glycogen deposition, then, could be, first, a synthesis of excess keratin, which could later be followed by proliferation.

Summary

Large quantities of glycogen are present in the epithelium of the vagina and vestibule at all ages.

Glycogen is normally absent in the epithelium of the labia minora and majora, except in the outer-root sheath of hair follicles.

Large quantities of glycogen are present in the epithelium of leukoplakia of the vulva.

Glycogen is not found in carcinoma of the vulva, except on the surface of some tumors, and in more differentiated areas of others.

References

1. Lillie, R. D.: Histopathologic Technic and Practical Histochemistry, Philadelphia, 1954, Blakiston Company, p. 274.
2. Hotchkiss, R. D.: Arch. Biochem. **16**: 131, 1948.
3. McManus, J. F. A.: Nature **158**: 202, 1946.
4. Leblond, C. P.: Am. J. Anat. **86**: 1, 1950.
5. Glick, D.: Techniques of Histo- and Cyto-Chemistry, New York, 1951, Interscience Publishers, Inc., p. 43.
6. Montagna, W., Chase, H. B., and Hamilton, J. B.: J. Invest. Dermat. **17**: 147, 1951.
7. Montagna, W.: Internat. Rev. Cytol. **2**: 281, 1952.
8. Bradfield, J. R. J.: Nature **167**: 40, 1951.
9. Rothman, S.: Physiology of Skin, Chicago, 1954, University of Chicago Press, p. 465.
10. Sasakawa, M.: Arch. Dermat. u. Syph. **134**: 418, 1921.
11. Way, S.: Malignant Disease of the Female Genital Tract, Philadelphia, 1951, Blakiston Company, p. 29.
12. Bullough, W. S.: Nature **165**: 493, 1950.

THE VALUE OF A PREPARED CULTURE MEDIUM IN THE DIAGNOSIS OF TRICHOMONAS VAGINALIS

WANDA H. WOLINSKA, NEW YORK, N. Y.

(From the Strang Laboratory of Cytology, Memorial Center for Cancer and Allied Diseases)

TRICHOMONAS vaginalis is the cause of numerous disorders of the female genitourinary tract.[4, 5, 9] Actual demonstration of the parasites is of great importance in diagnosing *T. vaginalis* infestation and in assessing the effects of treatment which is often prolonged. Furthermore, certain structural cellular changes in cervical and vaginal smears may be occasionally explained by the presence of the parasite.[1, 6, 8] The present work is concerned with the evaluation of a new medium for culturing *T. vaginalis* and with the comparison of these results with those obtained by other methods of detection.

Material and Methods

In the present study, 203 consecutive patients from the special gynecological service of the Strang Clinic were checked for the presence of *Trichomonas vaginalis* by three methods:

1. Culturing the vaginal fluid in Trichosel* medium.
2. Hanging drop.
3. Routine cytological smears.

Fluid from the posterior vaginal fornix was obtained by means of two cotton-tipped applicators. One applicator was immersed in 1 c.c. of warm saline for hanging-drop studies. The other applicator was immersed in 10 c.c. of previously prepared culture medium. Routine cervical and vaginal smears on each patient were stained by the Papanicolaou method.

Culturing of Trichomonas Vaginalis

The trypticase culture medium employed in the present work is a prepared powdered medium containing chloramphenicol for control of bacterial growth.[11]

Composition.—Formula in grams per 950 ml. of distilled water:

Trypticase	20.0
Cysteine hydrochloride	1.5
Maltose	1.0
Agar	1.0
Methylene blue	0.003
Chloramphenicol	0.1

pH 6.0±

Preparation of Medium.—Twenty-three and six-tenths grams of dehydrated material is dissolved in 950 c.c. of distilled water, mixed thoroughly, heated, stirred, and boiled for about one minute. Nine and one-half cubic centimeters

*A trypticase culture medium recently developed by Baltimore Biological Laboratory, Inc.

of the solution is dispensed into screw-top test tubes and autoclaved at 12 pounds pressure for about 15 minutes. Tubes are stored at room temperature. Just before it is used, 0.5 c.c. of human serum adjusted to pH 6.0 is added aseptically to each tube. Commercially available plasma, although having a pH of 7.0, may be used in lieu of serum, with comparable results.

According to the formula, if the medium is not used on the day of preparation, it should be reautoclaved or boiled for 2 to 3 minutes. In our experience, the medium stored at room temperature was still usable for as long as 3 weeks after preparation without repeated sterilization.

Cultures taken in the previously described manner do not require immediate incubation, but may be left at room temperature for several hours. Incubation overnight at 35-37° C. is necessary to stimulate the growth, however. The readings were obtained after 3, 24, or 48 hours.[3]

The reading is done in wet smears in vitro. The recognition of Trichomonas is based on the motility of the protozoa and the mobility of the undulating membrane. The presence of nonmotile organisms was not considered as a positive result. The highest number of motile parasites was usually found in cultures incubated 24 hours.

Two methods were used in control studies: the hanging-drop technique, and the routine cytological smears.

The Hanging-Drop Technique

The simplest and most commonly employed test for the detection of *T. vaginalis* is the hanging-drop method. The procedure is based on microscopic recognition of motile protozoa in a wet preparation. The method has the following disadvantages:

1. The preparation must be examined immediately.
2. The optimum temperature is 35-37° C.; with temperature variations the parasites may lose their motility.[10]
3. When there are only a few parasites in the preparation, they may be difficult to find or are obscured by the debris often present in vaginal fluid.

Trichomonas Vaginalis in Cytological Smears

Actual demonstration of the parasite in smears is essential. Its form is round or oval, sometimes slightly irregular; the outlines are not sharp. The size varies from that of a red blood cell to 20 μ.[9] When stained by the Papanicolaou method,[7] trichomonads usually appear as greenish-gray bodies with a small, dark nucleus. The presence of the nucleus is a helpful guide in differentiating *T. vaginalis* from degenerating polyps, degenerating nuclei, mucus, and debris. Cytological changes associated with Trichomonas infestation have been discussed elsewhere.[3, 5, 7, 8] The drawbacks of the cytological method in detection of the parasite are:

1. Confusion of the parasite with debris.
2. The relatively high degree of skill required of the microscopist for correct identification of the parasite.

Results

Trichomonads were conclusively demonstrated by at least one of the three methods employed in 24 of the 203 patients investigated. Table I summarizes the final results.

There were 179 negative reports by all three methods. In 5 of these cases, the smears were initially interpreted as harboring the parasite but this could

not be confirmed on review. The initial error of interpretation was based on cellular changes which are by no means specific. In 15 cases the parasites were demonstrated by all three methods.

In 6 instances, the hanging drop was negative, while the culture and smear readings proved the presence of trichomonads in the vaginal specimen.

In 2 cases, the smears failed to reveal the presence of parasites, whereas the two other methods were positive.

In one case the parasites were demonstrated in smears, while the culture and hanging drop were negative.

In summary, out of 24 cases of Trichomonas infestation, the diagnosis was missed on Papanicolaou smears in 2 cases; in one case the smear proved more sensitive than the culture and the hanging drop. Also, 5 false positive readings were obtained on cytological smears. The hanging-drop method failed 7 times, but there was only one failure of the culture medium.

TABLE I. COMPARISON OF THREE TECHNIQUES IN DETECTING TRICHOMONAS VAGINALIS IN 203 CASES

NO. OF CASES	CYTOLOGICAL SMEARS	HANGING DROP	CULTURE
179	Negative	Negative	Negative
15	Positive	Positive	Positive
6	Positive	Negative	Positive
2	Negative	Positive	Positive
1	Positive	Negative	Negative

Conclusions

These results show that although cytological smears and hanging drop give a fairly accurate estimation of the presence of *Trichomonas vaginalis*, the Trichosel culture medium provides us with by far the most accurate method of detecting the presence of the parasite. The ease with which the vaginal secretion may be cultured under ordinary laboratory conditions renders this method eminently desirable for widespread use.

The Trichosel culture medium was brought to our attention by Lieutenant Colonel Philip R. Carlquist of the Fourth United States Army Area Laboratory at Fort Sam Houston, Texas.

We are indebted to Dr. Henriette C. Vera, Chief Bacteriologist of Baltimore Biological Laboratories, Inc., for supplying us with the Trichosel broth used in this study.

References

1. Bechtold, E., and Reichner, N. B.: Cancer **5**: 442, 1952.
2. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations and Discharges, New York, 1953, Blakiston Company.
3. Kean, B. H., and Day, E.: AM. J. OBST. & GYNEC. **68**: 1510, 1954.
4. Kean, B. H.: AM. J. OBST. & GYNEC. **70**: 397, 1955.
5. Kean, B. H., and Wolinska, W. H.: Am. J. Clin. Path. **26**: 1142, 1956.
6. Koss, L. G., and Durfee, G. R.: Cancer **8**: 295, 1955.
7. Papanicolaou, G. N., and Wolinska, W. H.: Internat. Rec. Med. **168**: 551, 1955.
8. Pundel, J. P.: Les Erreurs de l'interprétation colpocytologique en présence du Trichomonas. Les Infestations à Trichomonas, Premier Symposium Européen, Paris, 1957, Masson & Cie, pp. 90-94.
9. Trussell, R. E.: Trichomonas vaginalis and Trichomoniasis, Springfield, Ill., 1947, Charles C Thomas, Publisher.
10. Vera, H. C.: Personal communication.
11. Baltimore Biological Laboratory, Inc.: New Trichosel Broth, Bulletin No. 01-489.

85

DIAGNOSIS OF TRICHOMONAS VAGINALIS VAGINITIS

THOMAS A. BURCH, M.D., CHARLES W. REES, PH.D., AND LUCY REARDON, M.A., BETHESDA, MD.

(From the Laboratory of Tropical Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare)

WHILE *Trichomonas vaginalis* may be associated with a severe incapacitating vulvovaginitis, it is usually, however, associated with a variable low-grade chronic vaginitis with increased vaginal discharge and itching or burning of the genitals with an occasional acute exacerbation.[2, 4]

Accurate diagnosis is important when the epidemiology or other aspects of trichomoniasis are investigated and especially when the results of chemotherapy are evaluated, since in the absence of complete eradication of the parasite a recurrence of *T. vaginalis* vaginitis can be anticipated[7] even when the possible role of an infected sexual partner is not taken into account.

While it has been previously reported that the culture technique is the most sensitive method of diagnosing *T. vaginalis*[6, 7, 10] it has been utilized in so few laboratories that a reiteration with additional data appears to be in order.

Material and Methods

Studies were made on 1,848 female employees of the National Institutes of Health who participated in one or more of 3 annual vaginal cytology surveys conducted by the National Cancer Institute. More detailed studies were made on 97 volunteers found to have trichomoniasis in the first survey or who were referred to the Trichomonas project because of vaginal discharge or itching.[3, 4]

The patients were instructed not to douche or use vaginal medication for 24 to 48 hours before examination. The vaginal secretion for the Papanicolaou smear, wet smear, and culture was obtained by means of a glass pipette with a rubber bulb. In the 1956 survey all three techniques were performed on the same vaginal sample in 499 women. In the remaining examinations only the Papanicolaou smear and culture were prepared from the same pipette sample.

Papanicolaou Smears.—The secretion was expelled onto a glass slide, spread and immersed immediately in equal parts of ether and absolute ethyl alcohol. The fixed smears were stained by Papanicolaou's method and the slides examined by the Washington Cytology Unit of the National Cancer Institute.

Wet Smear.—While the material for a wet smear is usually obtained by means of a cotton swab, in this study a small drop of vaginal secretion was expelled onto a dry glass slide (from the pipette used to make the Papanicolaou

smear), a drop of saline added, and the preparation was then examined immediately with a compound microscope (8 mm. objective) for the presence of the characteristically motile trichomonads.

Culture Method.—After these smears were prepared, the vaginal pipette was rinsed off in a tube of NIH trypticase-liver-serum medium (TLS) prepared as detailed hereafter. Vaginal cultures from volunteer study patients were made with a separate pipette rather than the one used for preparing the vaginal smears to avoid the possibility of contamination of the culture with fungus from the slides. A drop of sediment from the bottom of the culture tube was placed on a glass slide without a cover slip and examined in the same manner as a wet smear. The cultures were often given a "preliminary" examination within one to several hours after inoculation and then 2 or 3 times at varying intervals after incubation at 37° C. for 24 to 120 hours.

The medium used in these studies was originally developed to meet the need for agar-free cultivation and has been described briefly by Baernstein[1] in reporting on aldolase in *T. vaginalis*. The medium was a combination of 2 nutrient fluids with the addition of horse serum, a reducing agent, and antibiotics. Solution A contained: BBL trypticase 20 Gm., NaCl 7 Gm., dextrose 10 Gm., dissolved in 1 L. of distilled water and heated to 100° C. Solution B contained: Difco Bacto liver 50 Gm., infused in 1 L. of distilled water for 1 hour at 56° C., heated to 80° C., filtered through paper, volume brought to 1 L., to which was added NaCl 7 Gm., tryptone 5 Gm., KCl 0.4 Gm., $CaCl_2$ 0.4 Gm., and $NaHCO_3$ 0.4 Gm. The broth was then heated in the autoclave and filtered through paper. Six hundred milliliters of solution A was mixed with 1,000 ml. of solution B and then the pH adjusted to 6.0 with 5N HCl. The medium was dispensed into 16 by 150 mm. test tubes in 8 ml. amounts. Five-tenths milliliter of sterile unpreserved horse serum was added per tube after which the medium was stored at 37° C. for 24 to 72 hours as a check on sterility. The serum which was purchased from Difco laboratories was labeled as "sterilized by filtration"; however, it was further filtered through 0.03 Selas candles, rebottled, and stored in the refrigerator until used.

A reducing agent consisting of 0.2 ml. of a 4 per cent solution of sodium thioglycollate was added to each tube after inoculation of the vaginal specimen. The stock solution was made up in distilled water at weekly intervals, dispensed in test tubes in 10 ml. amounts, sterilized in the autoclave, sealed with paraffin, and stored at room temperature.

Penicillin and streptomycin were added to inhibit bacterial growth. Stock material was prepared in sterile physiological saline solution in the amount of 10,000 units or micrograms per milliliter, respectively, of penicillin G potassium and dihydrostreptomycin sulfate. For use the solution was diluted 1:10 and 0.4 ml. added per tube. The stock solution was kept frozen and the diluted solution refrigerated and used for no more than one week.

Results and Comment

Papanicolaou Smear.—The diagnosis of vaginal trichomoniasis as reported by the Washington Cytology Unit of the National Cancer Institute showed poor correlation with the results of the cultures in the 1956 survey. After the microscopists of the cytology unit restudied the smears from the 1956 survey in which the culture and cytology reports did not agree, their diagnoses improved and there was a better agreement between the results of the 2 tests in the 1957 survey.

In the 1956 survey, 46 of 104, or 44.2 per cent of those reported as having *T. vaginalis* by the cytology laboratory, had negative cultures, and 85 of 143,

or 59.4 per cent of the women in whom this parasite was demonstrated by culture, were not reported to have the infection by the cytology unit. In the 1957 survey only 12 of 68, or 17.6 per cent of those reported as having *T. vaginalis* by the cytology laboratory, had negative cultures. The proportion of false negative reports from smears, however, remained approximately the same (Table I).

The diagnosis of vaginal trichomoniasis by means of the Papanicolaou smears was less accurate than by the culture method. Fewer than half of the patients from whom *T. vaginalis* was cultured (114 of 266) were reported to have trichomoniasis on the basis of the Papanicolaou smear. While it is realized that the diagnostic acumen of the cytology technicians would improve with further review and training, it is doubtful that the smear method could approach the sensitivity or specificity of the culture technique. According to Papanicolaou and Wolinska[9] the cytology technicians at the Strang Cancer Clinic did not report *T. vaginalis* in 19 per cent of the patients from whom the parasite had been demonstrated by wet smears.

TABLE I. COMPARISON OF REPORTS OF T. VAGINALIS BY MEANS OF PAPANICOLAOU SMEARS AND THE CULTURE METHOD

SURVEY	T. VAGINALIS REPORTED ON PAPANICOLAOU SMEAR	T. VAGINALIS REPORTED BY CULTURE METHOD		TOTAL
		YES	NO	
1956	Yes	58	46	104
	No	85	798	883
	Total	143	844	987
1957	Yes	56	12	68
	No	67	824	891
	Total	123	836	959
Combined	Yes	114	58	172
	No	152	1,622	1,774
	Total	266	1,680	1,946

Wet Smears.—During the 1956 survey wet smears were prepared from the same pipette sample of vaginal secretion used to prepare the Papanicolaou smear and culture in 499 women. Trichomonads were not observed in 19 of 72, or 26.4 per cent of the women found to be infected by the culture method (Table II). In no instance was a patient positive by the saline suspension and negative by culture. Comparison of the wet smear with the Papanicolaou smear is probably not warranted on the data from the 1956 survey since, as shown previously, the Papanicolaou reports from that survey were less accurate than from the 1957 survey.

The wet smear or saline suspension was by far the simplest method for diagnosing vaginal trichomoniasis and while some investigators[2, 5] have considered it the method of choice, others[6, 7, 8] have considered it inferior to the culture method. In this connection it should be stated that when the wet smear is used it is very important that no lubricating jelly be used and that the patient not have douched or used any vaginal medication for at least 24 to 48 hours before the examination. These cause the trichomonads to round up and lose their motility[2] and it is by means of their characteristic movements that it is possible to recognize the trichomonads readily in a wet smear and differentiate them from leukocytes and other cellular elements.

Culture Method.—When the culture method was used, it made very little difference whether the patient had or had not douched. In fact, it did not

appear to matter very much if the patient had actually used one of the so-called trichomonacidal drugs, since, unfortunately, we have had no difficulty in culturing *T. vaginalis* during treatment with every therapeutic agent we have tried.

TABLE II. COMPARISON OF REPORTS OF T. VAGINALIS BY MEANS OF CULTURE, WET SMEARS, AND PAPANICOLAOU SMEARS IN THE 1956 SURVEY

T. VAGINALIS REPORTED BY			NUMBER OF PATIENTS
CULTURE	WET SMEAR	PAPANICOLAOU SMEAR	
+	+	+	33
+	+	0	20
+	0	+	3
+	0	0	16
0	+	+	0
0	+	0	0
0	0	+	15
0	0	0	412
	Total		499

Trussell[12] reported growth in his culture medium when but one trichomonad was inoculated per milliliter. We obtained growth when a single parasite was inoculated into a tube containing 8 ml. of culture medium by means of a Rees micromanipulator.[11] It is thus apparent that it is possible to demonstrate *T. vaginalis* by culture when there is but one parasite in the inoculum.

In addition to being the most sensitive of the various diagnostic techniques available, the culture method was also the most convenient, since a highly trained cytology technician was not needed, as in the case of the Papanicolaou smears, and the microscopic examination for the motile trichomonads did not have to be done immediately but could wait, within limits, the convenience of the examiner. Furthermore, the seeded culture could remain at room temperature for several hours, if an incubator was not readily available.

Kean and Day[6] stated that all positives would be detected if the culture were examined after 48 hours, and, if negative, re-examined after 96 hours' incubation. In a few patients, however, trichomonads were not observed until after 120 hours of incubation and occasionally the cultures from known positive women were entirely negative.

To ascertain the prevalence of false negative reports by the culture method, the results of 512 vaginal cultures from 56 volunteer women with confirmed vaginal trichomoniasis, who had had no treatment for at least one month, were analyzed. Trichomonads were not reported from 42, or 8.2 per cent, of the cultures from these known positive cases. In this connection it should be emphasized that the false negative cultures were not limited to asymptomatic women but occurred also in women with a definite vaginitis.

Summary and Conclusions

1. Accurate diagnosis of vaginal trichomoniasis is important when the epidemiology or other aspects of trichomoniasis are investigated and especially when the results of chemotherapy are evaluated.

2. Diagnosis by means of the Papanicolaou smears was the least sensitive and specific method in that fewer than half of the patients from whom *T. vaginalis* was cultured were reported to have trichomoniasis.

3. While the wet smear was the simplest, the culture method often demonstrated the infection when the wet smear was negative.

4. The culture method was more convenient than the wet smear method in that the microscopic examination did not have to be done immediately but could be deferred. It made little difference whether the patient had douched or recently used vaginal medication; if viable parasites were present, the culture method usually demonstrated them.

5. Examination of vaginal cultures at 48 and 96 hours demonstrated nearly all cases of infection. About 8 per cent of such cultures from known infected women were entirely negative, however.

6. Since some of the false negative cultures occurred in patients with definite vaginitis, a single negative examination should not rule out trichomoniasis in a woman with appropriate clinical findings.

7. The following procedure is recommended for the diagnosis of vaginal trichomoniasis:

a. Obtain a sample of vaginal secretion by means of either a cotton-tipped applicator or a vaginal pipette.

b. Inoculate the secretion into a tube of NIH TLS culture medium by inserting the applicator into the tube or rinsing out the pipette in the medium.

c. Add sodium thioglycollate and antibiotics as detailed under Methods.

d. Incubate the culture at 37° C. and examine a drop of sediment for motile organisms with the compound microscope, preferably at 24 hour intervals but at least at 48 and 96 hours.

e. If a preliminary examination is desired when symptoms are acute, the material in the cotton-tipped applicator can be removed from the culture tube and used to prepare a wet smear. In a similar manner, a wet smear can be prepared from the pipette at the time of inoculation.

We wish to thank Mrs. Violet Davis of the Section on Protozoal Diseases for assistance in the cultural diagnosis of *T. vaginalis*.

References

1. Baernstein, H. D.: Exper. Parasitol. **4**: 323, 1955.
2. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations, and Discharges, New York, 1953, Blakiston Company.
3. Burch, T. A.: Proc. First Pan-American Cancer Cytology Congress. (In press.)
4. Burch, T. A., Rees, C. W., and Kayhoe, D. E.: Am. J. Obst. & Gynec. **76**: 658, 1958.
5. Feo, L. G.: Am. J. Trop. Med. **5**: 786, 1956.
6. Kean, B. H., and Day, E.: Am. J. Obst. & Gynec. **68**: 1510, 1954.
7. Kupferberg, A. B.: Internat. Rec. Med. **168**: 709, 1955.
8. Papanicolaou, G. N.: Atlas of Exfoliative Cytology, Cambridge, Mass., 1954, Harvard University Press.
9. Papanicolaou, G. N., and Wolinska, W. H.: Internat. Rec. Med. **168**: 551, 1955.
10. Perl, G., Guttmacher, A. F., and Raggazoni, H.: Obst. & Gynec. **7**: 128, 1956.
11. Rees, C. W.: Problems in Amoebiasis, Springfield, Ill., 1955, Charles C Thomas, Publisher.
12. Trussell, R. E.: Trichomonas Vaginalis and Trichomoniasis, Springfield, Ill., 1947, Charles C Thomas, Publisher.

THE CHAIN SUTURE IN OPERATIVE GYNECOLOGY*

ROBERT TAUBER, M.D., PHILADELPHIA, PA.

(From the Graduate School of Medicine of the University of Pennsylvania)

IN 1952 my experimental studies for proper hemostasis in dissecting a bridge of tissue, such as the mesosalpinx, the mesenteriolum, the parametrium, and many others, revealed a very frequent but seldom recognized technical error. The first ligature around the free edge of a tissue bridge is correctly placed and tied. The second and the following ligatures, however, are erroneously tied into the gap which is created by the dissecting cut, leaving areas between the ties which are not ligated. These uncontrolled areas are the cause of many a hemorrhage (Fig. 1, *A* and *B*).

The Development of the Chain Suture

In 1953 I[2] suggested for the elimination of this drawback passing the suture through the tissue twice, in a kind of a mattress suture. One stitch around the tissue, which should be ligated, is called "the encircling stitch," and the other one, which is passed in opposite direction through the previously ligated tissue, the "stump stitch" (Fig. 1, *C*). Only a correctly applied stump stitch offers a perfect hemostasis. The needle must go through the entire thickness of the stump, close to the previous stitch canal (Fig. 1, *C*).

It is generally known that tissue always retracts in the moment when it is dissected. Then it is difficult to place the stump stitch correctly. Often it proves impossible to pick up more than a small fraction of the stump and naturally the hemostasis will be defective. The correct placing of the stump stitch, namely, as mentioned before, through the entire thickness of the stump and close to the previous stitch canal, can be accomplished only by passing the stump stitch first, and dissecting the ligated tissue afterward.[3]

The correct placing of the stump stitch is not the only consideration for setting the time of the dissection. It is also of the greatest importance to expose the tissue for the following encircling stitch as much as possible. A sufficient exposure can be achieved only if the previously ligated tissue is dissected before the encircling stitch is applied. The best time for the dissection is therefore *after* the stump stitch and *before* the encircling stitch. The loss of the ligature from the needle at the time of the dissection is eliminated by using the ligature with an attached needle. This 27 inch long suture material prompted us to switch from the individual mattress stitches to a continuous suture technique, which we call chain suture technique. The significant feature of the chain suture is that each "link" of the chain, created by the stump stitch and the encircling stitch, is tied individually.[4] Therefore, a finished chain suture consists of a chain of ligature loops which are connected by square knots (Fig. 2, *E*).

*Presented at the Second World Congress, International Federation of Gynecology and Obstetrics, Montreal, Quebec, June 22-28, 1958.

In order to use the chain suture successfully it is indispensable to try and practice the new technique on a 4 by 4 inch gauze pad which is fixed on a training board[5] or any other wooden base, with three thumb tacks as shown in Fig. 2, *B*. Two lines *C* and *D* are drawn with ink on the gauze pad, about 1 cm. apart and parallel to each other. *C* indicates the line where the chain suture should be placed, and *D*, the line of the dissection. A half-circle needle of medium size, furnished with a 60 inch long ligature of twine or any other material, may be used for practicing. The ligature is doubled all the way and the ends are tied together; thus the ligature cannot escape from the needle eye during the dissection. The "doubled suture" is excellent for training if catgut sutures with attached needles are not available.

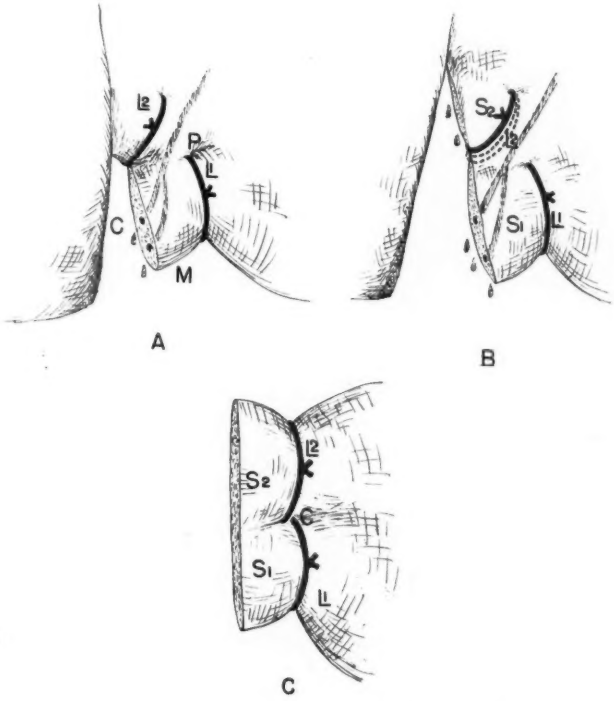


Fig. 1.—The hidden error in dissecting a bridge of tissue.

A, The first ligature *L1* has been placed correctly. The second ligature *L2* is erroneously tied into the gap created by the separating cut *C*.

B, The separating cut has been extended. The second stump *S2* is tapering. The ligature *L2* slips (dotted lines) and gets loose, causing a bleeding of the second stump *S2*. The area between the ligatures *L1* and *L2* is not ligated. A blood vessel passing this unligated area is causing a bleeding even from the first well-ligated stump *S1*.

C, The stump stitch. The ligature *L2* is correctly passed through the stump *S1*, close to the previous stitch canal *C*. There is no unligated area between the ligatures *L1* and *L2*. The hemostasis is perfect.

Practicing the Chain Suture

The first stitch is made in the line *C* from back to front encircling the free edge of the pad (Fig. 2, *A*). This suture is pulled through the stitch canal leaving the free end 7 inches long (the length of an average needle holder). The ligature is tied but, contrary to the ordinary routine, the ligated tissue is not cut. The dissection is postponed until the suture has been passed through the ligated tissue from front to back (Fig. 2, *B*: the stump stitch). Now is the

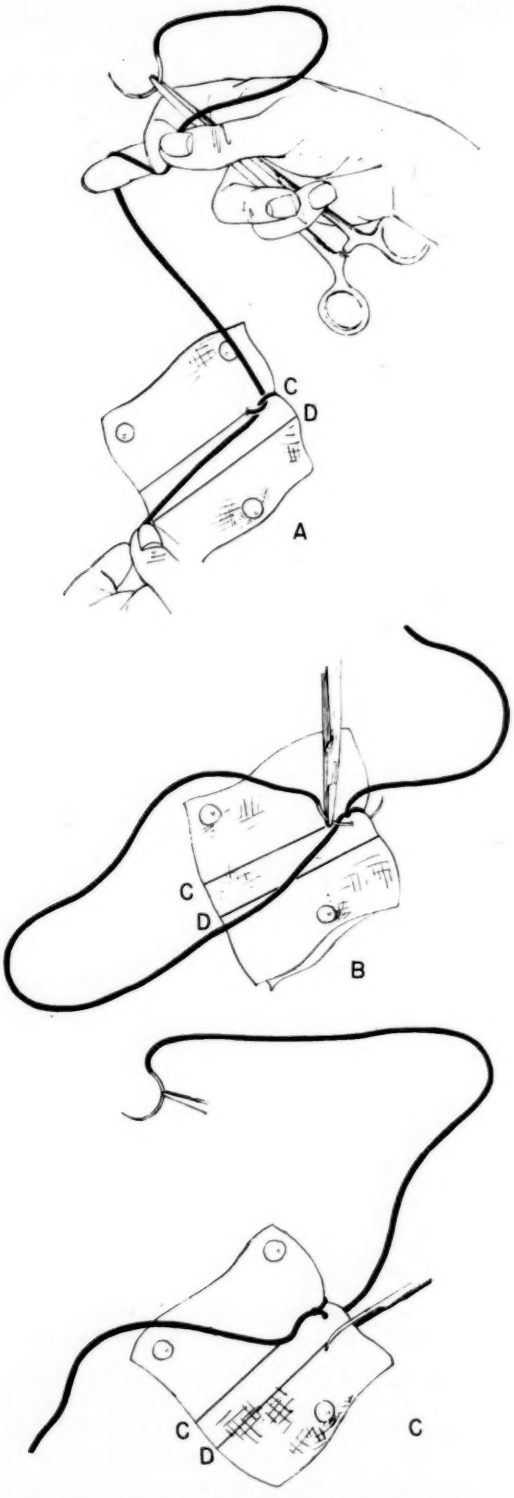


Fig. 2.—*A-C, For lengends see opposite page.*

right time for the dissection, namely, *after* the stump stitch and *before* the stitch which encircles with the same suture the next section of the tissue bridge from back to front (Fig. 2, *C*). The ligature is tied with the free end used again, and the needle is passed through the previously ligated tissue from front to back (stump stitch). The dissection is extended in the line *D*; the encircling stitch follows (Fig. 2, *D*). The steps are repeated in the correct sequence: encircle, tie, pass, cut, encircle, tie, and so on until the entire bridge of tissue is dissected.

The superiority of the chain suture over the clamp technique can readily be realized from Table I.

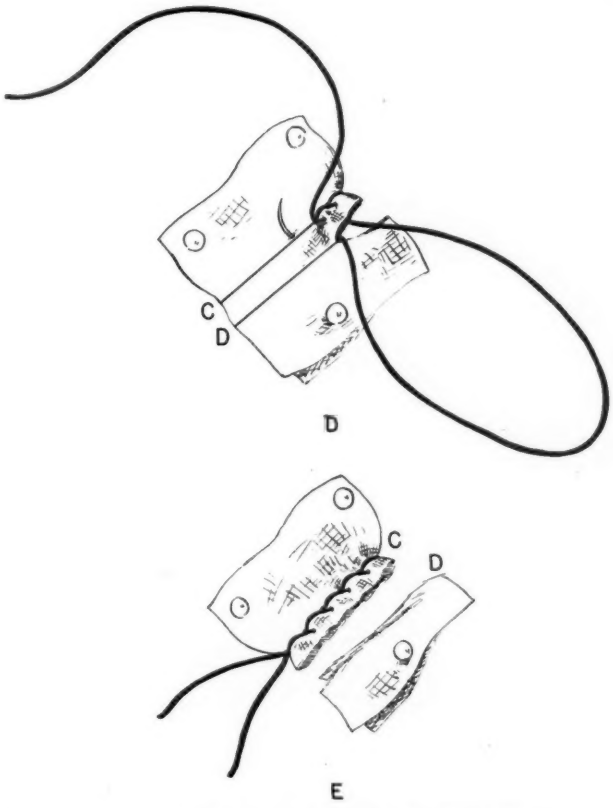


Fig. 2.—*C*, Line of the chain suture. *D*, Line of the dissection.

A, Start of the chain suture. The first stitch has encircled the edge of a 4 by 4 inch gauze pad in the line *C* from back to front. The ligature is tied.

B, The stump stitch. The needle is passed close to the stitch canal through the ligated tissue from front to back.

C, The ligated tissue is cut in the line *D*.

D, The following section of the gauze pad has been encircled with the same needle in the line *C*. The ligature has been tied and the needle passed through the ligated tissue close to the previous stitch canal. The dissection has been extended in the line *D*. A new section of the tissue is encircled with the needle in the line *C*.

E, The steps—encircle, tie, pass, cut—have been repeated. The entire bridge of tissue has been ligated in the line *C* by a chain of loops which are connected by square knots. The dissection in the line *D* is completed.

Many bridges of soft tissue can readily be dissected by the chain suture technique in the same way as shown on the gauze pad. No further technical details have to be added to an uncomplicated salpingectomy or a salpingo-oophorectomy. An appendectomy is greatly facilitated by the chain suture

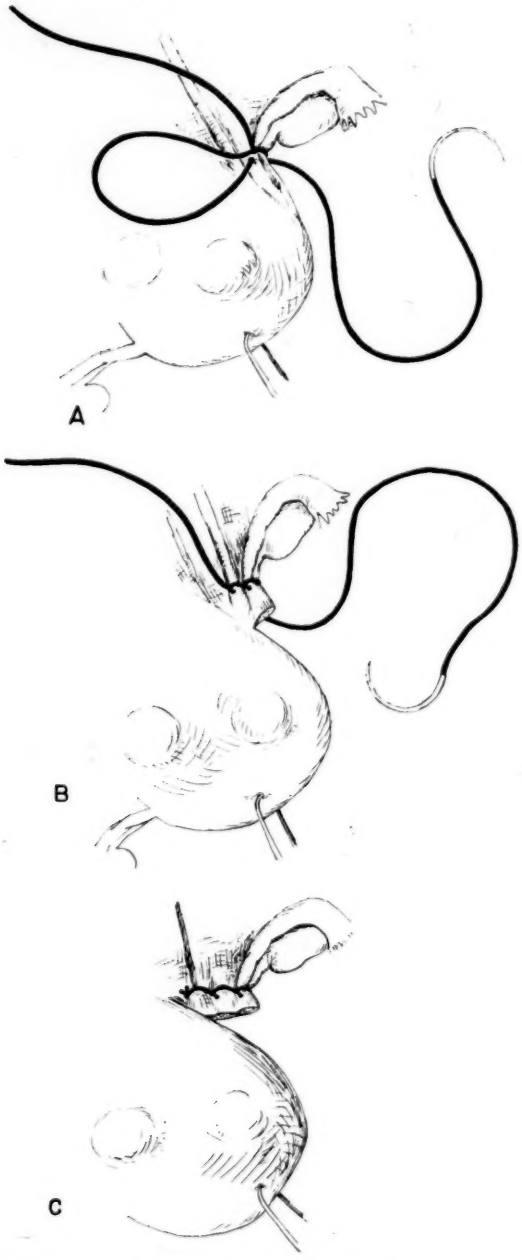


Fig. 3.—Ligation of the adnexa and the parametrium.

A, The first suture ligature with the attached needle has been applied and tied around the right tube and the ovarian ligament. The same suture is passed, as stump stitch, through the ligated tissue close to the stitch canal from front to back.

B, The ligated tube and ovarian ligament have been dissected. The round ligament has been encircled and tied. The needle is passed through the ligated round ligament from front to back, close to the previous stitch canal (stump stitch).

C, The parametrium which includes the right uterine vessels has been encircled and tied with the same suture ligature. Both ends are cut off. The ligated tissue which includes the uterine vessels is not dissected.

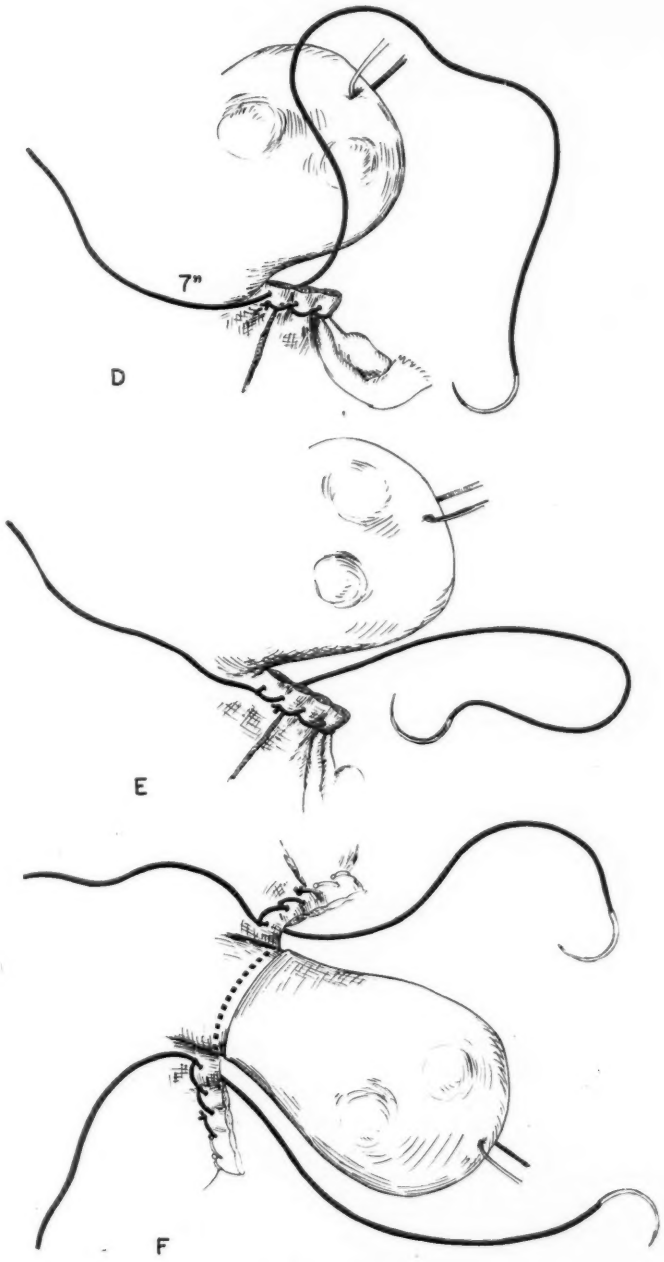


Fig. 3.—*Cont'd.*

D, The second suture with the attached needle has been passed as stump stitch through the ligated parametrium which includes the left uterine vessels. The ligated tissue is dissected.

E, The following parametrium has been encircled, tied, and passed by the stump stitch. The ligated tissue is dissected.

F, The uterosacral ligaments have been encircled and tied. The stump stitch is passed through the ligated tissue on either side. The ligated ligaments are not dissected.

technique if the mesoappendix is shortened or indurated or edematous. The hidden apex of an appendix which requires a retrograde appendectomy is readily exposed by a step-by-step dissection of the mesoappendix. No crushing clamps are used which damage the fragile tissue and narrow the limited operating field.

How to ligate the adnexa and the parametrium in the total abdominal hysterectomy with the chain suture, and how a single suture takes care of the hemostasis of the vaginal cuff and the peritonization of the stumps will be presented in the following section.

TABLE I

CHAIN SUTURE	CLAMP TECHNIQUE
1. The tissue is safely ligated first and dissected afterward.	1. The clamped tissue is dissected first and ligated afterward. This sequence implicates a certain risk.
2. An accidental break of the ligature cannot cause a hemorrhage because no tissue is dissected before it is ligated.	2. An accidental break of the ligature, which has to replace the clamp, is frequently the cause of annoying and often dangerous bleeding.
3. The hemostasis does not depend on an instrument.	3. The hemostasis depends for some time on the condition of the clamp.
4. The chain suture cannot slip.	4. The ligatures which replace the clamps slip frequently along the line of the cut.
5. There are no areas between the ties which could remain unligated.	5. The "hidden error" creates unligated areas between the ties, which are a common cause of hemorrhage during and after the operation.
6. The stumps consist of sound tissue, and are therefore dependable.	6. The stumps consist of tissue damaged by crushing clamps.

The Technique of the Total Hysterectomy

The intra-abdominal work starts with the separation of the bladder from the cervix.

A catgut No. 1 suture ligature with an attached round needle encircles the right tube and the right ovarian ligament from back to front. The tissue which has to be ligated is first encircled, immobilized, and supported with the bridge clamp,[3] which makes the placing of the encircling stitch, distal to the bridge clamp, safer and easier, especially if the accessibility is poor. The bridge clamp has no hemostatic effect and is removed as soon as the needle has passed the tissue. The ligature is pulled through the stitch canal until the free end is 7 inches long. The ligature is tied and the needle passed immediately through the ligated tissue from front to back as stump stitch (Fig. 3, *A*). A reflux clamp is placed close to the edge of the uterus and the ligated tissue is dissected.

The round ligament is encircled by carrying the same suture ligature through the avascular area of the broad ligament from back to front. The ligature is tied with the same free end (Fig. 3, *B*), and passed immediately through

Fig. 4.

A, Right angle stitch. The uterus has been removed. The right needle suture *R* is passed through the posterior and anterior vaginal walls close to the angle of the vagina.

B, Hemostasis of the vaginal cuff. The angle stitches have been tied, and the short, free ends of the ligatures have been cut off. The edge of the posterior vaginal wall *P* is sutured with the suture *L*, and the edge of the anterior vaginal wall *A* is sutured with the suture *R*.

C, The safety suture. The suture *R* encircles as a continuous suture the left line of the dissection in front of the chain suture, and the suture *L* the right one.

D, Peritonization. The peritoneum is closed over the stumps with the same sutures *R* and *L* returning to the center. The needles are cut off and the ligatures are tied together.

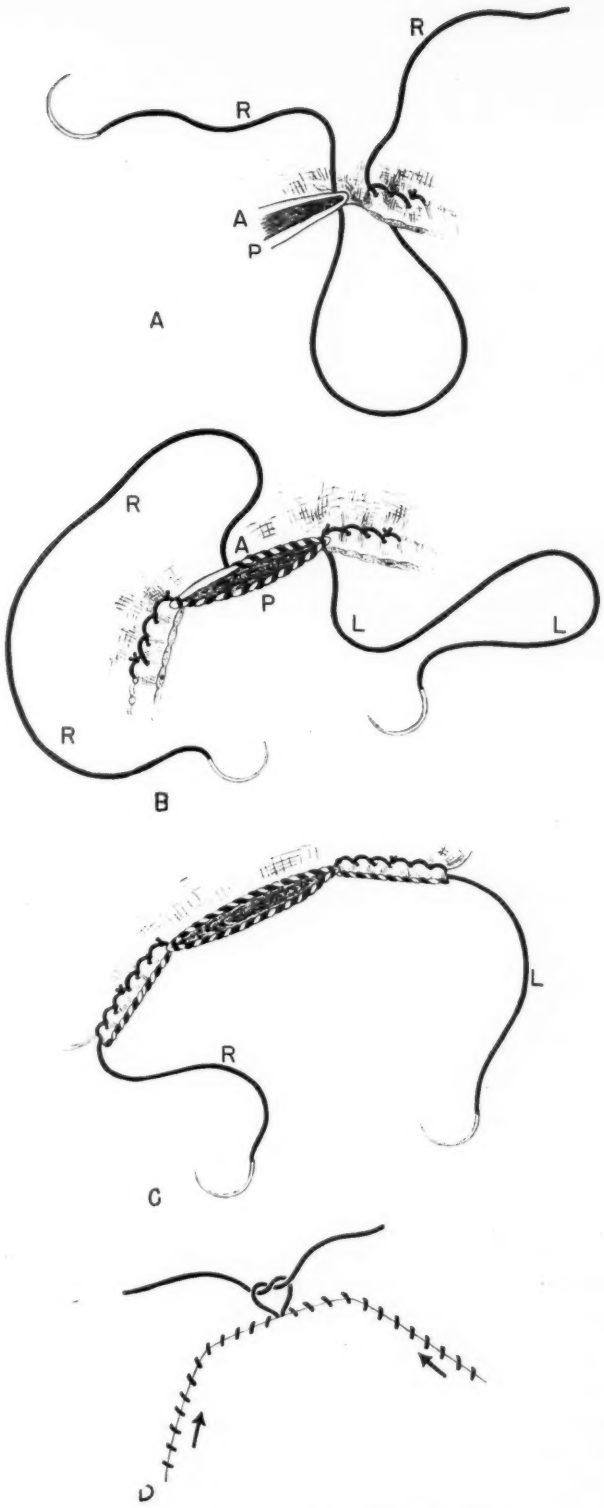


Fig. 4.—*For legend see opposite page.*

the ligated round ligament from front to back (stump stitch). A reflux clamp is placed close to the uterus, and the round ligament is dissected (Fig. 3, *B*). The following stitch encircles the right uterine artery. Here the embracing bridge clamp protects the blood vessels from being injured by the needle point. The bridge clamp is removed after the encircling stitch, and the ligature is tied. Both ends of the suture are cut off.

It is a blood-saving technique to postpone the dissection of the uterine vessels until the uterine artery on the other side has been ligated.[1] Thus no reflux clamp on either side is necessary, and the dissection can be made close to the edge of the uterus—an important advantage because of the proximity of the ureter.

The balance of the first suture ligature which carries the needle is used for the ligation of the adnexa, the round ligament, and the uterine vessels on the left side. After the ligation of the left uterine vessels the suture is cut off without dissection of the last ligated tissue (Fig. 3, *C*). All reflux clamps are removed because no reflux bleeding is expected after the ligation of both uterine arteries.

The second catgut suture with the firmly attached needle is passed as stump stitch from front to back through the ligated section of the parametrium which includes the left uterine artery, leaving the free end of the ligature 7 inches long. The previously ligated tissue, including the left uterine vessels, is dissected (Fig. 3, *D*). The following section of the left parametrium is encircled with the same suture and tied. The needle is passed immediately as stump stitch through the last ligated parametrium which is then dissected. The steps, encircle, tie, pass, cut, are repeated as many times as necessary, depending on the extension and condition of the parametrium (Fig. 3, *E*). Finally, the uterosacral ligament is encircled, tied, and the stump stitch is passed, but the ligament is *not* dissected. A hemostat is applied to the short, free end of the suture ligature and the long end with the needle stays in place for later use.

The third ligature with the attached needle is passed as stump stitch, through the ligated section of the parametrium which includes the right uterine artery, and the ligated tissue is dissected. The same steps as on the left side—encircle, tie, pass, cut—are performed on the right side until the suture has been passed through the right uterosacral ligament as stump stitch (Fig. 3, *F*).

Circular incisions around the cervix dissect the pericervical fascia and as many fibers of the uterosacral ligament as necessary to flatten the vaginal vaults. The vagina is opened and the uterus removed.

The right suture ligature, *R*, which is still in place, is passed first through the posterior and then through the anterior wall of the vagina, thoroughly including in each stitch the vaginal mucosa (Fig. 4, *A*). The ligature which encircles the right angle of the vagina, called "angle stitch,"[3] is tied. The left angle stitch is made with the left suture, *L*, which is continued as running suture around the posterior wall (*P*) of the vagina for hemostasis (Fig. 4, *B*). The right suture, *R*, takes care of the anterior vaginal wall in the same way. The hemostatic sutures around the edges of the vagina move the suture *L* to the right and the suture *R* to the left side. Each one continues as a running suture along the line of the dissection as the so-called safety suture. The stitches are passed through the stumps of the parametrium and the adnexa distal to the previous chain suture (Fig. 4, *C*). They achieve additional hemostasis along the entire line of the dissection.

Peritonization.—After the safety suture the peritoneum is closed over the stumps with the same sutures *R* and *L* returning to the midline. The needles are cut off and the ligatures are tied together (Fig. 4, *D*).

Summary

1. The step-by-step development of the new chain suture is outlined, and the technical details described and illustrated.

2. The superiority of the chain suture over the clamp technique is discussed.

3. The chain-suture technique for the salpingectomy, salpingo-oophorectomy, and appendectomy is demonstrated.

4. The technique of the total hysterectomy is presented in detail, and the combination of the chain suture with the new safety suture is shown.

5. The technique of performance with a single suture is presented: (a) the ligation of the parametrium, (b) the angle stitch, (c) the hemostasis of the vaginal cuff, (d) the safety suture, and (e) the peritonization of the parametrial stumps.

References

1. Tauber, R.: Am. J. Obst. & Gynec. 63: 1272, 1952.
2. Tauber, R.: Am. J. Obst. & Gynec. 65: 1111, 1953.
3. Tauber, R.: Am. J. Obst. & Gynec. 68: 1160, 1954.
4. Tauber, R.: J. Albert Einstein M. Center 3: 5, 1954.
5. Tauber, R.: Basic Surgical Skills, Philadelphia, 1955, W. B. Saunders Company.

2019 Walnut Street, Philadelphia 3, Pa.

A NEW CLAMP FOR THE MARSHALL-MARCHETTI OPERATION

LOUIS A. BUNIM, M.D., BROOKLYN, N. Y.

(From the Obstetrical and Gynecological Service {Third Division}, Bellevue Hospital, and the Department of Gynecology, New York University College of Medicine)

IN PERFORMANCE of the Marshall-Marchetti operation for stress incontinence technical difficulties are encountered in placing the periurethral sutures. Traction on the Foley bulb as viewed in the space of Retzius may result in an injury to the anterior wall of the bladder and thus the bladder cavity is accidentally entered.

For the operator or his assistant to push the anterior wall of the vagina up, to demonstrate the position of the urethra with its Foley catheter, not only is difficult but can easily result in contamination of the operative field.

To facilitate the procedure I have tried a Babcock clamp to lift up the urethra with the enclosed catheter and have successfully visualized the periurethral space and was then able to place the sutures in the desired position. The Babcock clamp has a sharp terminal edge which can be closed completely, however. The bladder was entered at the bulb in one particular instance. It is true that one can easily repair the small rent without ill effects, but the surgeon will have to keep the Foley catheter in for a longer period of time to secure proper healing.

The clamp* as herein presented will, it is felt, greatly facilitate the exposure and deliver the urethra with its catheter in situ. It is advisable to place the retropubic sutures first, then deliver the urethra by gently lifting the enclosed catheter with the new clamp. The sutures are placed ¼ of an inch lateral to the urethra. The clamp is so constructed as not to close completely and possesses rounded edges to avoid bladder or urethral injury.

Fig. 1 demonstrates the original Marshall-Marchetti operation.

Fig. 2 demonstrates the new clamp in situ.

Fig. 3 demonstrates the urethral clamp.

*Manufactured by J. Sklar & Co., Long Island City, N. Y.

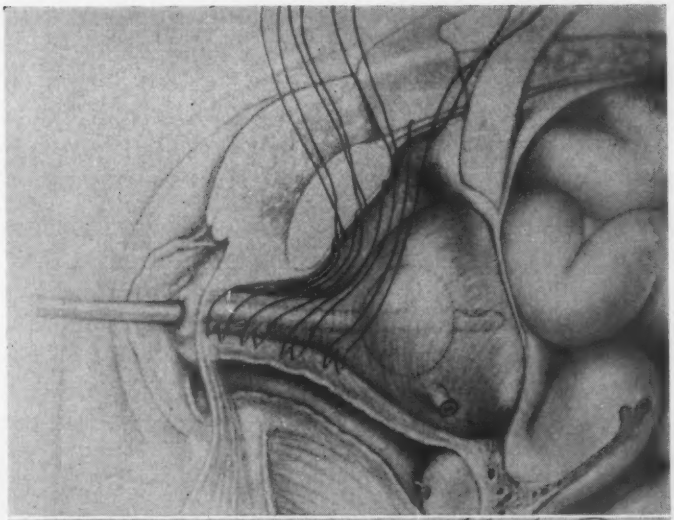


Fig. 1

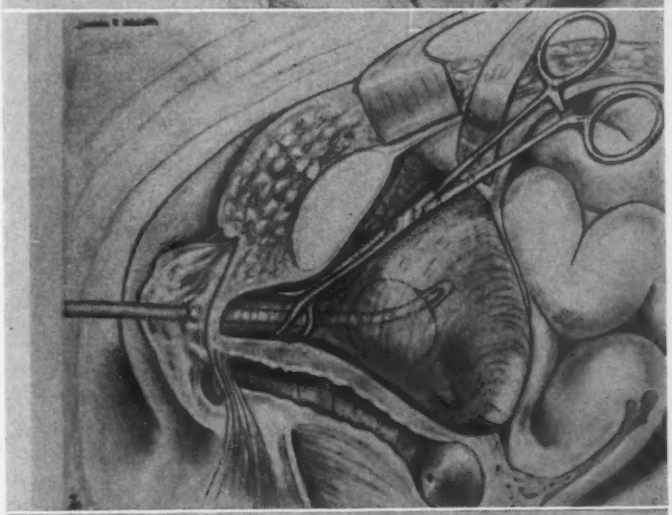


Fig. 2.

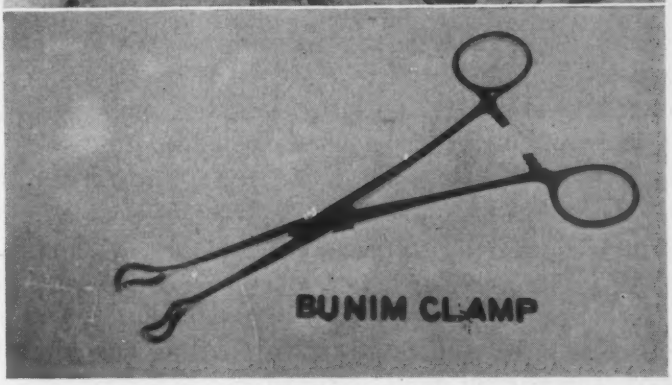


Fig. 3.

Fig. 1.—Sagittal section showing location of the four paraurethral sutures on the left. (From Marshall, Marchetti, and Krantz.[1])

Fig. 2.—Use of the clamp to elevate the urethra with Foley catheter in place.

Fig. 3.—The urethral clamp.

Reference

1. Marshall, V. F., Marchetti, A. A., and Krantz, K. E.: Surg. Gynec. & Obst. 88: 509, 1949.

Obstetrics

SERUM PROTEIN, LIPID, AND LIPOPROTEIN FRACTIONS IN NORMAL HUMAN PREGNANCY*†

ELIZABETH KNAPP SMITH, PH.D.,** RUSSELL R. DE ALVAREZ, M.D., AND JEAN FORSANDER, M.A., SEATTLE, WASH.

(From the Department of Obstetrics and Gynecology, University of Washington Hospitals and School of Medicine)

SERIAL studies of distribution of plasma proteins during normal pregnancy, by the moving boundary method of electrophoresis, have been reported previously by Macy and Mack,[1] Lagercrantz,[2] and others. Significant alterations from normal adult levels were found in almost all fractions, with changes progressing to a maximum late in the third trimester. Albumin and gamma globulin decreased, whereas the alpha globulins, beta globulin, and fibrinogen increased. Values returned to normal after delivery.

Likewise, numerous investigators[3-5] have shown that an increase in serum lipid concentration occurs in normal pregnancy as well as in disorders of pregnancy, such as pre-eclampsia and eclampsia. Boyd[4] and Peters and associates[5] have reported increases in serum cholesterol, cholesterol esters, phospholipid and neutral fat, with maximum values attained late in the third trimester.

In recent years it has been found that a major portion of the serum lipids is bound to protein, especially to the alpha and beta globulins, forming the alpha and beta lipoproteins. The beta lipoproteins contain most of the cholesterol. Anderson and Keys[6] have found a high correlation between the serum beta lipoprotein concentration determined by paper electrophoresis and cholesterol concentration in normal man. Interest in the lipoproteins of serum has been accelerated by the reports of Gofman and co-workers[7] that the S_f10-20

*This investigation was supported, in part, by Research Grant No. H-2474, from the National Institutes of Health, United States Public Health Service.

†Presented at a meeting of the Western Society for Clinical Research, Carmel, Calif., Jan. 31, 1958.

**Department of Pathology, Children's Orthopedic Hospital, Seattle 5, Wash.

lipoproteins, determined by ultracentrifugation, are elevated in patients with atherosclerosis. Gofman's group has implicated these lipoproteins in the etiology of atherosclerosis and coronary heart disease. We have been interested in the possible relationship of the increased concentration of serum lipids and lipoproteins observed in pregnancy to the hypertension of toxemia of pregnancy and to subsequent hypertensive disease.

Since the changes seen in normal pregnancy, in both protein and lipid distribution, are accentuated in disorders of pregnancy, especially in the toxemias,[1, 3] it is important to have accurate data regarding the normal to use as a base line for discussion and interpretation of results obtained in the abnormal situation.

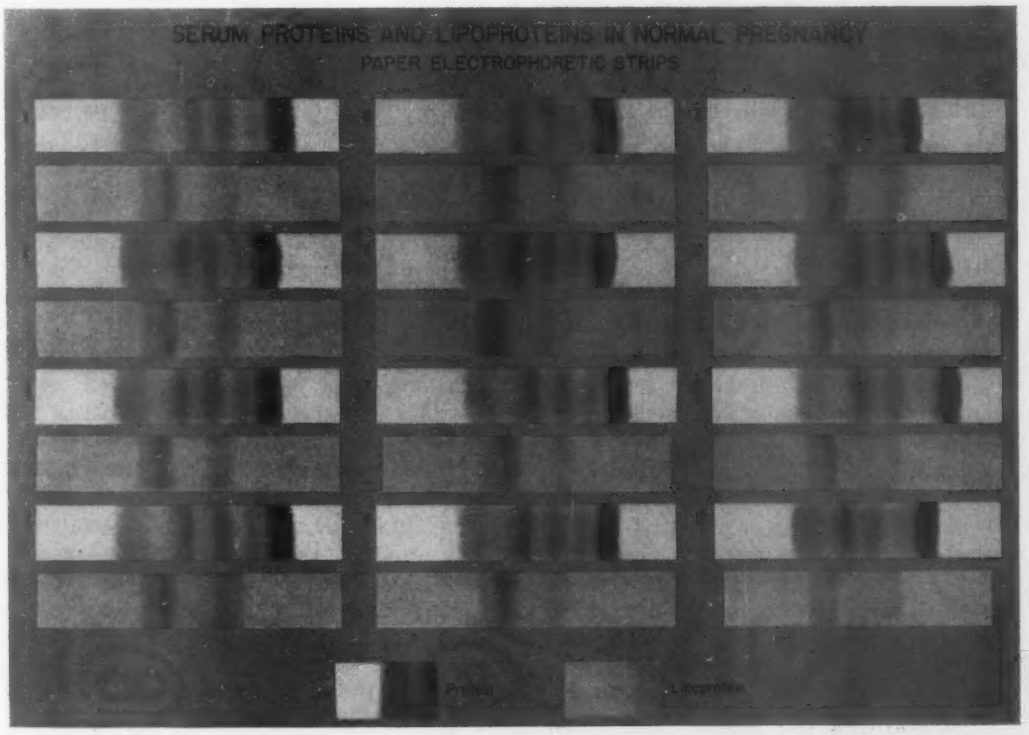


Fig. 1.—Paper electrophoresis strips of serum protein and lipoprotein distribution in Patient D. K. Strips were s ained with bromphenol blue for proteins, and oil red O for lipoproteins. Strips Nos. 1-8 represent determinations at 5, 10, 15, 19, 23, 27. 31, and 34 weeks of pregnancy; strips Nos. 9-12 represent determinations at 9 hours, 4 days, 7 and 15 weeks post partum, respectively.

Russ, Eder, and Barr[8] studied the protein and lipid relationships in plasma from pregnant women at delivery and the cord blood of their newborn infants after fractionating the plasma according to Cohn's method. Serial studies of simultaneous determination of protein, lipid, and lipoprotein distribution throughout the period of gestation and postpartum recovery have not been reported, however.

The present study was undertaken to determine the pattern of progressive change in serum proteins and lipids during normal pregnancy. With the

use of the newer techniques of paper electrophoresis, which require very small amounts of serum, it is possible to determine serum protein and lipoprotein distribution together with serum lipids determined chemically in the same patient at the same time. Initially 10 women observed longitudinally at approximately monthly intervals during normal pregnancy and the puerperium formed the study group. During the course of the investigation one of our laboratory technicians, who had volunteered to serve as a nonpregnant control, became pregnant. We were fortunate in obtaining a blood sample and analysis on this patient at the fifth week of pregnancy before the diagnosis of pregnancy was suspected. She was then followed at frequent intervals throughout the pregnancy, delivery, and early and late postpartum periods. Thus, the opportunity was provided of studying the serial changes in protein and lipid distribution in pregnancy in relation to the nonpregnancy "control" level in the same patient. The data obtained on this patient are representative of the data obtained on the larger group of patients, and since the data on this patient are complete in themselves, they have been made the principal subject of this presentation.

Materials and Methods

The patient, Mrs. D. K., was a healthy, well-developed, well-nourished white woman, 25 years of age, who weighed 148 pounds and was 5 feet, 9 inches tall. She was in the above-average economic level, consuming a good diet, probably somewhat above average in fat content. The pregnancy, her first, was entirely uncomplicated, except for early delivery. She was delivered at 36 weeks of a healthy female infant weighing 5 pounds, 5 ounces. Her postpartum recovery was entirely normal; she did not attempt to nurse her infant.

While it was not possible to procure blood samples during the fasting state, they were consistently obtained at approximately 4 hours after a light breakfast. The fat content of the general diet was not regulated. All analyses, except total lipid, were carried out promptly on the fresh serum.

Electrophoretic separation of serum proteins and lipoproteins was carried out by Durrum's[9, 10] method, with the hanging strip apparatus supplied in the Spinco Model R paper electrophoresis system. Distribution of the proteins was determined after the paper strips were stained with bromphenol blue. Lipoprotein distribution was determined as described by Jencks[11] with oil red O for staining the lipids. The amount of dye bound by each of the separated protein fractions was estimated by direct optical scanning of the strips, not oiled and not treated with ammonia, with the Spinco Analytrol with B-3 cam to record simultaneously the optical density and integral curves. For the lipoprotein strips a 0.6 neutral density filter was placed in the rear filter holder along with the blue filter. Results were expressed in terms of the bromphenol blue and oil red O dye binding capacity of the separated fractions. Protein and lipid patterns of the same serum were traced on one graph for comparison of the resultant curves. The protein pattern serves as a guide for allocation of the lipoprotein components.

In many cases the beta lipoprotein peak was split, thus providing the possibility of calculating a value for the "O" fraction,[12] which represents chylomicrons and trailing beta lipoprotein, and which approximates the neutral fat fraction. The split peak was not a uniform finding, however, hence only alpha and beta lipoproteins were routinely calculated. Since the sum of alpha and beta is 100 per cent, the values for beta lipoprotein are the reciprocals of those for alpha lipoprotein.

Total protein in the serum was determined by the biuret method[13] with purified human serum albumin as a standard, the concentration of which was determined by micro-Kjeldahl nitrogen analysis with the factor 6.25 used to convert to protein concentration.

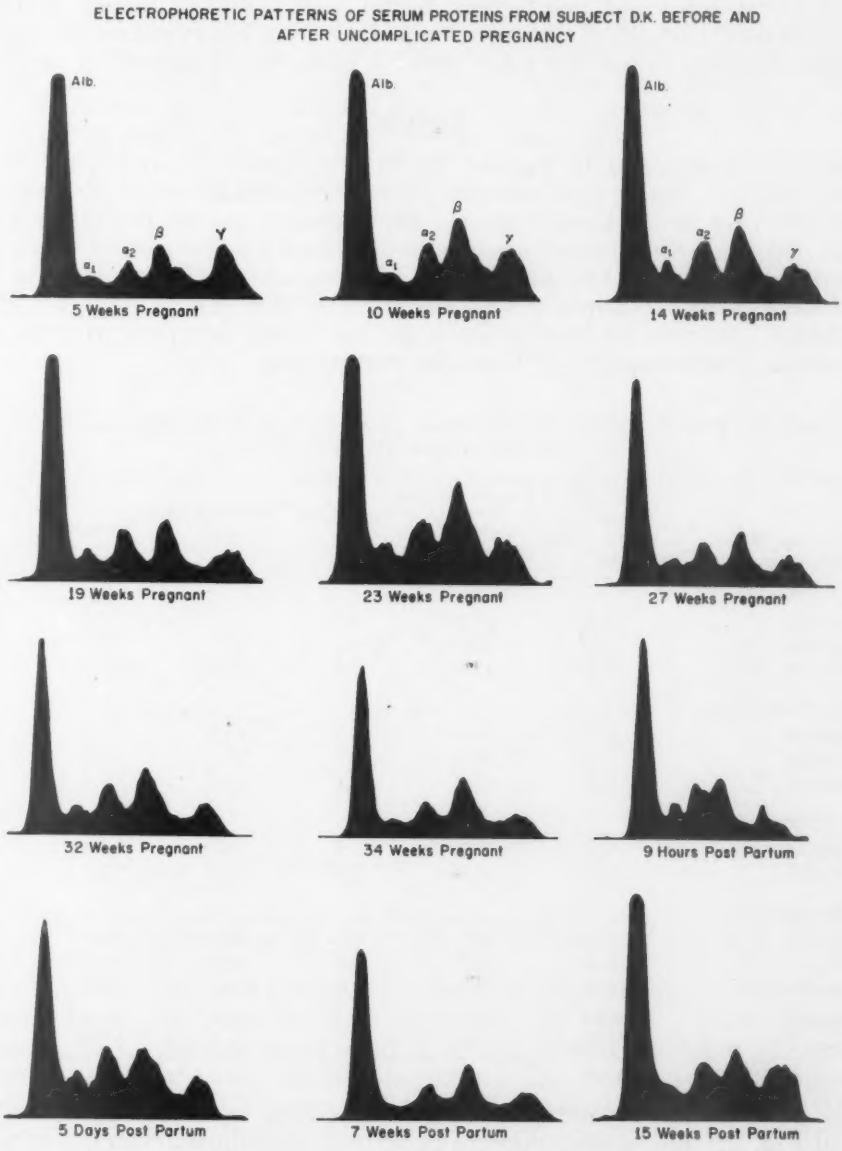


Fig. 2.—Protein electropherograms corresponding to the stained paper strips presented in Fig. 1. Tracings were obtained with the Spinco Analytrol with B-3 cam.

It should be emphasized that the concentration of each serum protein fraction is expressed in terms of per cent of the total protein rather than as grams of protein, to avoid the error introduced by multiplying per cent values obtained in one set of units (dye-binding capacity) by total protein concentration in another set of units (biuret value). Lipoproteins also are expressed as per cent of total dye-binding capacity; these values cannot readily be converted to absolute concentrations.

Cholesterol, total and free, was measured by the digitonin method of Sperry and Webb,[14] slightly modified. Serum lipid phosphorus was determined as described by Hawk and associates.[15] Phospholipid values may be obtained by multiplying the figures for lipid phosphorus by a factor of 25. Total lipid was determined according to Sperry and Brand[16] on samples preserved by freezing. In some cases insufficient serum was available, hence heparinized plasma was used instead of serum. Comparative studies revealed no significant difference between values for total lipid on heparinized plasma or serum.

Results

The results obtained in Patient D. K. are illustrated in Figs. 1 to 4 and Tables I and II. Fig. 1 presents the paper strips obtained by electrophoresis and stained with bromphenol blue for the proteins and oil red O for the lipoproteins. Strips 1-8 represent samples obtained at 3 to 4 week intervals during pregnancy, starting at the fifth week of pregnancy and continuing to the thirty-fourth week. Sample 9 was obtained on the day of delivery, 9 hours post partum. Sample 10 was obtained on the fourth day post partum, sample 11 at 7 weeks, and sample 12 at 15 weeks post partum.

TABLE I. SERUM PROTEIN DISTRIBUTION IN PATIENT D. K. DURING AND AFTER UNCOMPLICATED PREGNANCY

PERIOD OF PREGNANCY	TOTAL PROTEIN (GM./100 ML.)	GLOBULINS (%)				
		ALBUMIN	ALPHA$_1$	ALPHA$_2$	BETA	GAMMA
First Trimester.—						
5 weeks	7.40	55.3	4.7	9.7	17.0	13.7
10 weeks	7.28	51.5	4.5	12.0	19.0	13.0
15 weeks	7.18	47.6	6.9	13.4	20.1	11.9
Second Trimester.—						
19 weeks	6.42	50.8	6.5	14.2	17.4	11.2
24 weeks	7.36	47.9	5.7	12.1	21.4	13.0
28 weeks	6.73	45.2	7.4	14.3	20.5	12.7
Third Trimester.—						
32 weeks	7.35	39.3	7.9	16.0	23.3	13.7
34 weeks	7.29	41.0	5.9	13.9	27.1	12.4
Post Partum.—						
9 hours	7.83	42.1	8.0	16.9	20.1	13.0
4 days	6.60	34.9	10.0	17.0	26.0	12.1
7 weeks	6.82	45.4	1.5	15.1	22.5	15.7
15 weeks	8.07	46.0	5.7	14.0	16.1	18.2
6 months	6.82	50.3	4.2	11.1	17.9	16.6

The protein electropherograms corresponding to the stained strips are shown in Fig. 2. The actual changes in protein distribution during pregnancy are better illustrated by the percentages of various protein fractions calculated from the areas under the curves which are given in Table I. The changes in distribution with duration of pregnancy for total protein, albumin, alpha$_2$ and beta globulin are also illustrated in Fig. 3. The data in Table I and Fig. 3 demonstrate that the percentage of serum albumin decreased as pregnancy advanced. The lowest level was attained on the fourth day post partum, but increased markedly at 7 weeks post partum. It had not yet reached the early pregnancy level of 55 per cent by 15 weeks or even 6 months post partum, however. The value of 55 per cent at 5 weeks of pregnancy is high compared

with that of our group of normal nonpregnant women, the average for 16 young women being 51.5 per cent. Concomitant with the decrease in albumin was an increase in both alpha$_1$ and alpha$_2$ globulin. At the same time, the percentage of beta globulin increased from 17 per cent at the fifth week of pregnancy to 27 per cent at the thirty-fourth week and had returned to 16.1 per cent at 15 weeks post partum. The alpha$_1$ globulin increased sharply in the immediate postpartum period to a maximum of 10 per cent, practically disappeared from the serum sample obtained 7 weeks post partum, and then appeared at normal values 15 weeks and 6 months post partum. The percentage of gamma globulin showed very little change except for an increase above nonpregnancy levels in the late postpartum period.

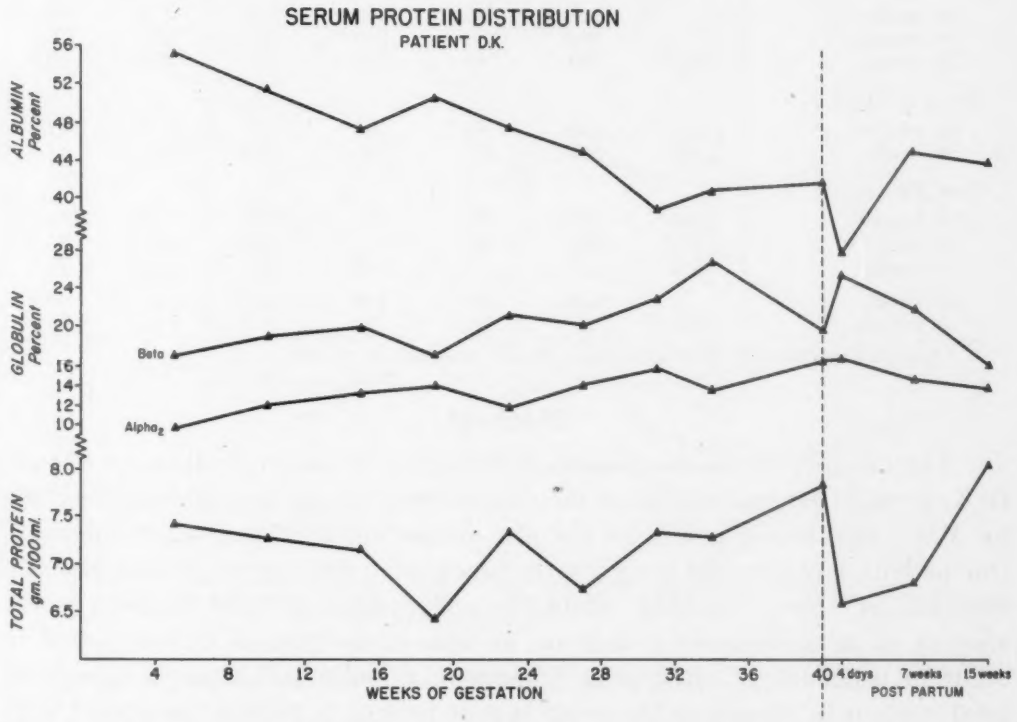


Fig. 3.—Serial changes in distribution of total serum protein, albumin, alpha$_2$ globulin, and beta globulin during pregnancy and post partum in Patient D. K.

The data for lipid and lipoprotein distribution during and after pregnancy in Patient D. K. are illustrated in Table II and Fig. 4. It is obvious that cholesterol, both free and ester, and lipid phosphorus increase as pregnancy progresses, reaching their maxima at term. The return to normal nonpregnancy levels is slow, with values still slightly elevated 6 months after delivery. Although the data for total lipids are incomplete, a progressive increase to a maximum in the early puerperium and a decline post partum are readily apparent from the figures in Table II. The percentage of alpha lipoprotein showed a decline with the progress of pregnancy, especially during the third trimester. A minimum value of 18.4 per cent was reached at 34 weeks of pregnancy. The value remained low during delivery and the early puerperium, increased slightly by 7 weeks post partum, increased further by 15 weeks, and had returned to early pregnancy levels by 6 months post partum. The early pregnancy value of 35 per cent alpha lipoprotein in this patient was slightly higher than the mean of 31.4 per cent for 16 normal nonpregnant women.

TABLE II. SERUM LIPID AND LIPOPROTEIN DISTRIBUTION IN PATIENT D. K. DURING AND AFTER UNCOMPLICATED PREGNANCY

PERIOD OF PREGNANCY	LIPID (MG. PER 100 ML.)					LIPOPROTEIN (%)	
	TOTAL LIPID	CHOLESTEROL			LIPID PHOSPHORUS	ALPHA	BETA
		TOTAL	FREE	ESTER			
First Trimester.—							
5 weeks		164	45	119	9.6	35.0	65.0
10 weeks		211	57	154	10.8	33.5	66.5
15 weeks	975*	257	73	184	13.3	31.0	69.0
Second Trimester.—							
19 weeks		228	53	175	14.1	37.6	62.4
24 weeks		280	80	200	17.8	27.5	72.5
28 weeks	1,313*	304	89	215	17.1	36.5	63.5
Third Trimester.—							
32 weeks	1,388*	283	80	203	17.3	22.5	77.5
34 weeks	1,388	298	85	213	17.3	18.4	81.6
Post Partum.—							
9 hours	1,500*	350	99	251	20.1	18.6	81.4
4 days	1,475	305	87	218	17.1	18.9	81.1
7 weeks	875*	279	77	202	12.3	24.7	75.3
15 weeks		225	67	158	14.4	31.1	68.9
6 months	913	231	55	176	11.3	34.1	65.9

*Analyses performed on heparinized plasma instead of serum.

Comment

The changes in electrophoretic distribution of serum proteins in Patient D. K. were, in general, similar to those reported for a group of pregnant women by Macy and co-workers with the use of moving boundary electrophoresis. Our patient, however, did not show the progressive decrease in gamma globulin reported by them. Perhaps related to our gamma globulin findings is the absence of as pronounced a decrease in total serum protein as is reported to occur in pregnancy.[16] Reduction of gamma globulin and albumin as well as total protein in plasma in the nonpregnant patient is usually associated with dietary protein deficiency. History, personal observations, and evaluations of dietary intake indicated that our patient consumed very liberal amounts of protein during pregnancy and was in excellent nutritional health. Hence, the reduction in albumin observed in D. K. is probably attributable more directly to physiologic alterations occurring in pregnancy, such as increased blood volume, etc., than to protein deficiency.

The sharp increase in alpha$_1$ globulin which occurred immediately post partum is of special interest. Chanutin and Gjessing[17] observed a fall in plasma albumin and a rise in the fast-moving globulins in dogs which suffered traumatic injury or destruction of tissue by injection of nitrogen mustards. As suggested by Macy,[1] the traumatic injury of labor or the rapidly occurring involution of uterine musculature following delivery might have a similar effect and thus be responsible for decreased albumin and increased alpha$_1$ globulin observed at this time in the recently pregnant patient.

The decrease in serum alpha lipoprotein (and therefore simultaneous increase in beta lipoprotein) seems to correlate well with the increase in cholesterol and lipid phosphorus which occurred in D. K. during pregnancy. The highest values for cholesterol (total, free, and ester) were attained on the day of delivery, whereas alpha lipoprotein reached its minimum at 34 weeks and remained low during the first 4 days post partum. Anderson and Keys[6] reported that the beta lipoprotein cholesterol (lipoprotein separated by paper electrophoresis) represented 81 per cent of the total cholesterol in serum.

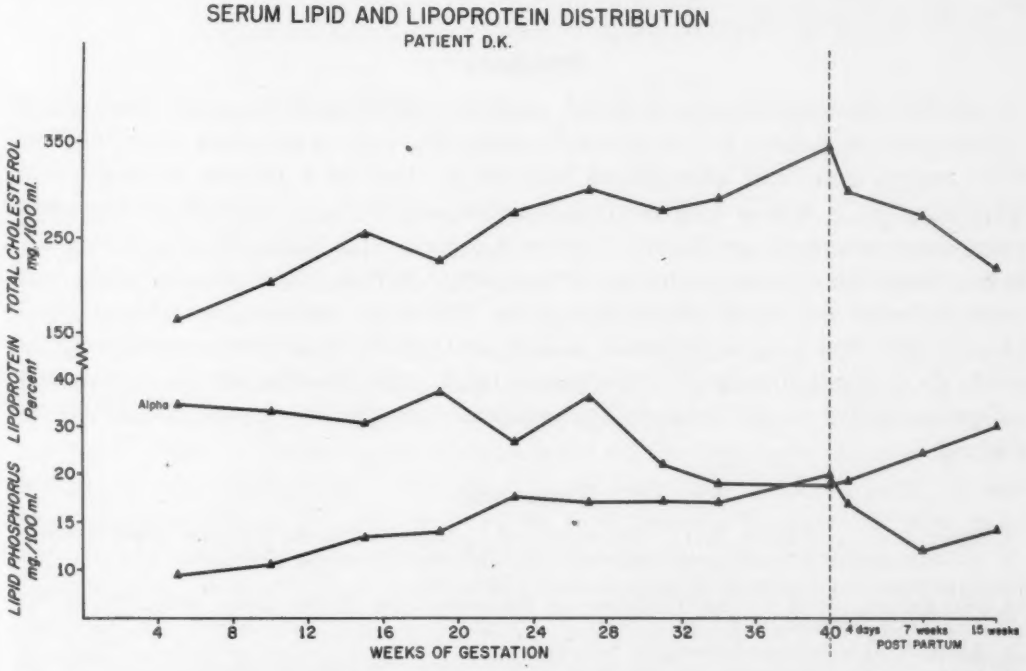


Fig. 4.—Serial changes in distribution of serum lipid fractions: total cholesterol, cholesterol esters, and lipid phosphorus during pregnancy and post partum in Patient D. K.

Hence, an increase in beta lipoprotein would be expected to occur in pregnancy as the concentration of cholesterol and cholesterol esters rises. Russ and co-workers[8] reported that the amount of cholesterol and phospholipid combined with alpha lipoprotein was diminished and the amount combined with beta lipoprotein relatively increased at delivery. In our patient the lipoprotein distribution returned to normal somewhat more rapidly than did the concentrations of cholesterol and lipid phosphorus.

The delay in the return of serum protein distribution to normal after delivery, demonstrated by D. K., is in agreement with the findings of Macy and Mack[1] who reported that at 6 to 12 weeks post partum the mean concentrations of albumin and the various globulins were still anywhere from 3 to 20 per cent different from the means for nonpregnant women. A similar delay in return to normal nonpregnancy levels was observed in our patient in respect to the serum lipids, cholesterol, lipid phosphorus, and the lipoproteins. In the group of 8 women studied serially during pregnancy and post

partum by Peters and collaborators,[5] the cholesterol concentration was slow in returning to normal. In only one of our 8 women was the concentration at 6 to 12 weeks post partum equal to early pregnancy levels for the same patient, but these workers suggest that there may be a decrease in lipid concentration in early pregnancy followed by the increase in late pregnancy. Our findings together with those reported by others indicate that a very long period is required for physiologic and metabolic readjustment with respect to protein and fat metabolism after pregnancy is completed, and tend to suggest that the period required for systemic involution is longer than the usually accepted 6 weeks post partum.

Summary

Serial determinations of total serum protein, protein, and lipoprotein distribution measured by paper electrophoresis, and serum cholesterol, cholesterol esters, and lipid phosphorus have been made in a normal primigravida beginning at 5 weeks of gestation, continuing at monthly intervals during pregnancy, and post partum at 9 hours, 4 days, 7 and 15 weeks, and 6 months. Serum albumin decreased during pregnancy, whereas the alpha globulins and beta globulin increased progressively to delivery. Serum cholesterol, lipid phosphorus, and beta lipoprotein, as well as total lipid, also increased progressively to a maximum early in the puerperium. All the changes were reversed following delivery, but most values required 6 months to return completely to normal.

References

1. Macy, I. G., and Mack, H. C.: Physiological Changes in Plasma Proteins Characteristic of Human Reproduction, Detroit, 1951, Children's Fund of Michigan.
2. Lagercrantz, C.: Upsala läkaref. förh. **51**: 116, 1945.
3. Dieckmann, W. J.: The Toxemias of Pregnancy, ed. 2, St. Louis, 1952, The C. V. Mosby Company, p. 126.
4. Boyd, E. M.: J. Clin. Invest. **13**: 347, 1934.
5. Peters, J. P., Heinemann, M., and Man, E. B.: J. Clin. Invest. **30**: 388, 1951.
6. Anderson, J. T., and Keys, A.: Clin. Chem. **2**: 145, 1956.
7. Gofman, J. W., Jones, H. B., Strisower, B., and Tamplin, A. B.: Circulation **14**: 691, 1956.
8. Russ, E. M., Eder, H. A., and Barr, D. P.: J. Clin. Invest. **33**: 1662, 1954.
9. Jencks, W. P., Durrum, E. L., and Jetton, M. R.: Biochem. J. **60**: 205, 1955.
10. Williams, F. G., Pickels, E. G., and Durrum, E. L.: Science **121**: 829, 1955.
11. Jencks, W. P., Jetton, M. R., and Durrum, E. L.: J. Clin. Invest. **35**: 1437, 1955.
12. Aldersberg, S., Rossak, E. T., Sher, I. H., and Sobotka, H.: Clin. Chem. **1**: 18, 1955.
13. Weichselbaum, T. E.: Am. J. Clin. Path. Tech. Supp. **10**: 40, 1946.
14. Sperry, W. M., and Webb, M. A.: J. Biol. Chem. **187**: 97, 1950.
15. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, Philadelphia and Toronto, 1947, The Blakiston Company.
16. Sperry, W. M., and Brand, F. C.: J. Biol. Chem. **213**: 69, 1955.
17. Chanutin, A., and Gjessing, E. C.: J. Biol. Chem. **165**: 421, 1946.

UNUSUAL OVARIAN CHANGES (HYPERTHECOSIS) IN PREGNANCY

MATTHEW J. G. LYNCH, M.B., M.R.C.P., LOND., F.C.A.P.,
PAUL R. KYLE, M.D., STANLEY S. RAPHAEL, M.B., B.S., LOND., AND
PATRICK BRUCE-LOCKHART, M.B., M.R.C.O.G., SUDBURY, ONTARIO

(From the Departments of Pathology, Obstetrics and Gynecology of The General Hospital, Sudbury)

INTEREST in the ovarian theca (interna) cell was greatly heightened by the description of the polycystic (sclerocystic) ovary syndrome by Stein and Leventhal[1] and by Robinson[2] in 1935. Both of these descriptions had the further merit that they advanced a surgical treatment in the form of wedge resection which has stood the test of time and given excellent results over the years.[3] Review of the literature shows, that, though spontaneous pregnancy in cases of the Stein-Leventhal syndrome is exceedingly rare, it does, nevertheless, occur.[1, 4, 5] There appears to be no knowledge of the histologic changes in such ovaries during pregnancy, however. Indeed, the only instance (and in this case the diagnosis is not certain!) where some account is given of what may happen clinically to these ovaries during gestation is that described briefly by Culiner and Shippel[6] of a woman who developed pronounced masculinizing signs in the latter months of pregnancy. The physician who delivered her by cesarean section noted that her ovaries were 5 times the normal size. Examination under an anesthetic 6 months later revealed that they had become smaller by two thirds.

Whereas it is generally agreed that there is some hyperplasia of theca interna cells during normal pregnancy[7, 8] the extent and degree are not at all clearly defined, nor is its significance understood. Therefore, it seems worth while recording the following 3 cases which, though dissimilar in some respects, all showed a most inordinate degree of theca-cell hyperplasia associated with gestation.

Methods and Material

Surgical and autopsy specimens were fixed in buffered neutral formalin. Paraffin sections were stained by hematoxylin and eosin, Masson's trichrome, Hotchkiss-McManus periodic acid-Schiff technique, and Foot's silver impregnation, while frozen sections were prepared from the fixed material and stained by oil red O.[9]

CASE 1.—A 29-year-old white gravida, i, para 0, was first seen in May, 1953, when she was 4 months pregnant, complaining of right lower quadrant pain of sudden onset. Torsion of an ovarian cyst was suspected and a trial treatment by bed rest instituted. The pain

quickly subsided, and conservative treatment was continued; but 4 weeks later there was a recurrence of similarly located pain, this time more severe and accompanied by nausea. The pain was not relieved for any length of time by 100 mg. of Demerol. Other relevant clinical findings were moderate hirsutism of the face, arms, chest, and abdomen, and a voice that was somewhat deeper in tone than average. The blood pressure was 120/80. The menarche had occurred between 14 and 15 years of age, and was followed by very irregular periods up to the time of conception. Overgrowth of hair was noted at the age of 18 years. She had been married 3 years and had never practiced contraception.

On June 30, 1953, a twisted right ovarian cyst the size of an orange was easily removed. At operation the left ovary did not appear remarkable. On the evening following removal of the cyst the patient went into labor and was delivered of a 5 months' fetus that died within a few minutes.

Fig. 1.—Blocks from enlarged ovary removed during pregnancy from Case 1, arranged so as to give some idea of actual size.

Pathologic Description.—Gross : The specimen consisted of a firm, diffusely enlarged ovary, 3¼ by 2 by 1¾ inches, weighing 59 grams. It was yellowish in color, and the cut surface showed a grayish-yellow, solid fleshy core rimmed by small cysts (0.1-0.6 cm.) beneath a thickened, opaque cortex (Fig. 1).

Microscopic: The cysts were of follicular type, though the granulosa layer was atrophic in most and had completely vanished in many. There was no evidence of luteinization of the granulosa cells. The most striking feature, however, was the enormous hyperplasia and marked "luteinization" of the theca cells surrounding all follicles (Fig. 2). These theca layers were from 5 to 30 cells thick. The cells themselves were very regular, cuboido-polygonal in outline, and less than half the size of the cells of the corpus lutem of pregnancy, which was present in the specimen (Fig. 3). They had a uniformly distributed, fine, moderately dense chromatin and prominent nucleoli. The cytoplasm was markedly eosinophilic and so

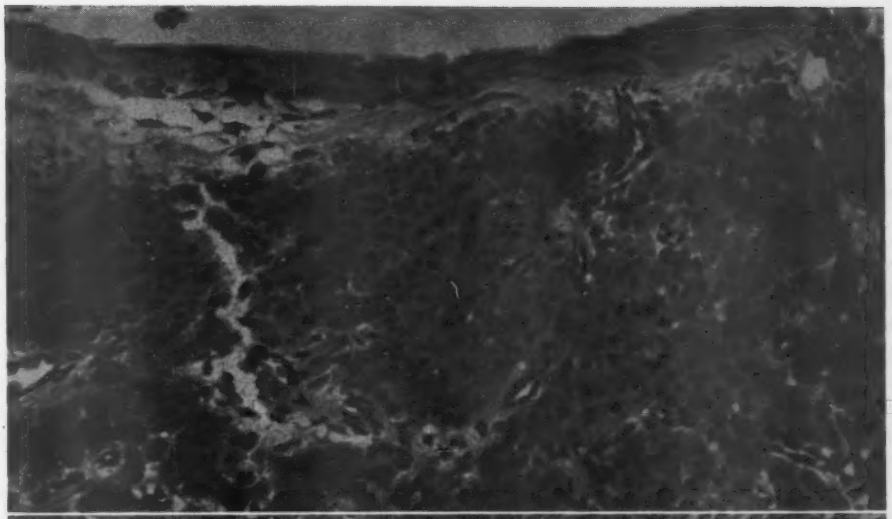


Fig. 2.

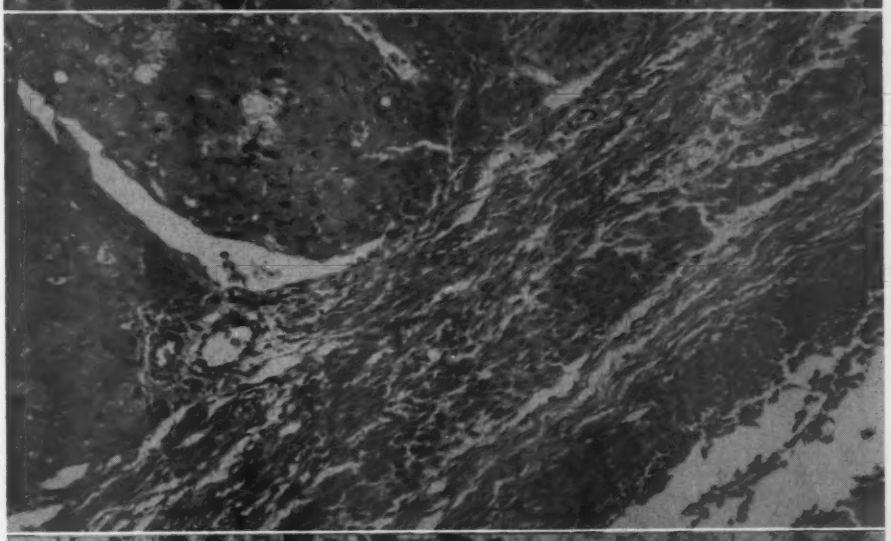


Fig. 3.

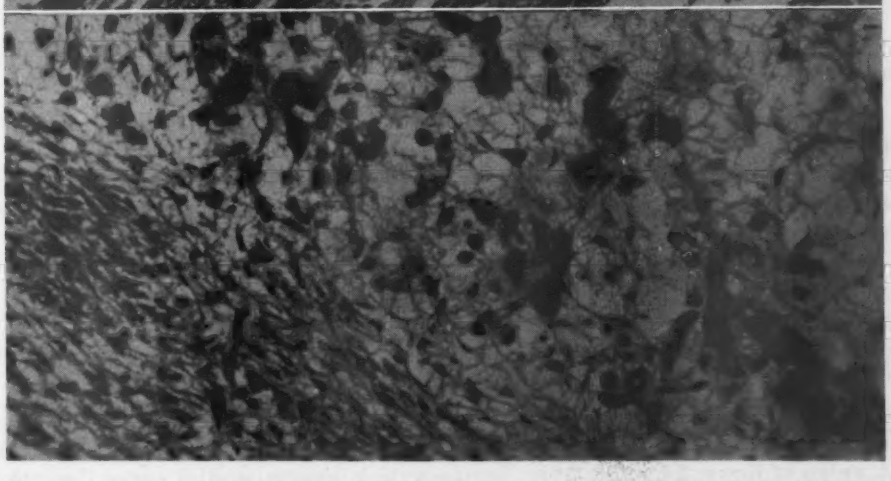


Fig. 4.

Fig. 2.—Case 1. Ovary removed during pregnancy; great hyperplasia and "luteinization" of theca interna cells; atrophy of granulosa. (Hematoxylin and eosin. ×300; reduced ⅓.)

Fig. 3.—Same as Fig. 2 to show luteinized theca cells in comparison with corpus luteum of pregnancy. (Hematoxylin and eosin. ×180; reduced ⅓.)

Fig. 4.—Same as Figs. 2 and 3. Luteinized theca cells in cicatrix of atretic follicle. (Hematoxylin and eosin. ×300; reduced ⅓.)

finely granular as to be almost homogeneous. Irregular clusters of similar cells were seen in the loose cicatrices of atretic follicles (Fig. 4), and deeper in the edematous ovarian stroma trabeculae of like cells were commonly seen. These theca cells appeared to have a negligible lipid content since they stained in a brownish hue with oil red O. They were seen to be surrounded by a fine meshwork of reticulin fibers on silver staining.

Further Course.—On Jan. 14, 1954, the patient was again hospitalized, this time 28 weeks pregnant and in labor and bleeding profusely from a partial placenta previa. The membranes were ruptured, and a 2 pound, 14 ounce female infant was delivered by breech delivery. The infant died after 2 days, but was normal except for being premature.

Following this her periods were regular for the first time in her life, and in February, 1956, she was delivered of a normal male 8 pound, 4 ounce baby (alive and well, and fully male, including the chromosomal sex pattern as determined on buccal scrapings, at the time of writing). The patient was subsequently well until September, 1956.

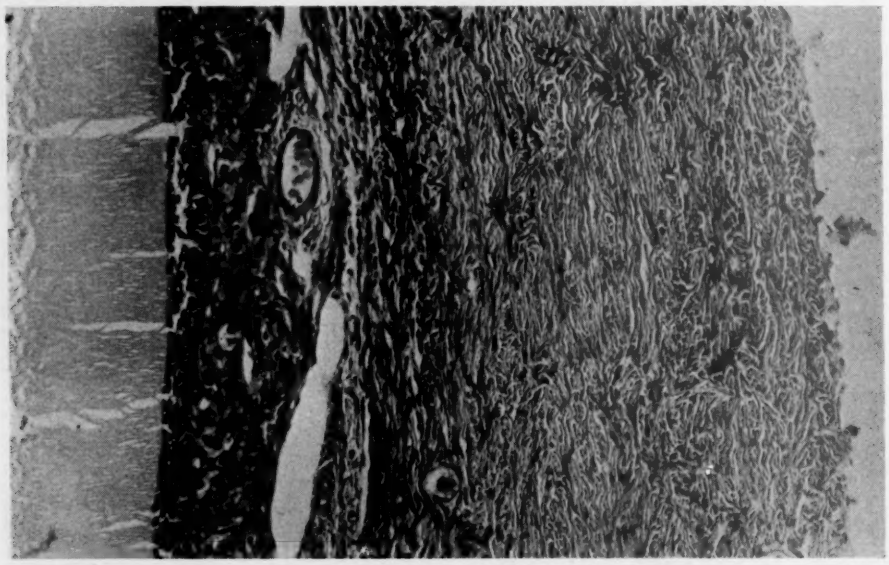


Fig. 5.—Section from wedge removed from second ovary in Case 1, showing typical sclerocystic picture. follicle cyst with luteinized theca beneath sclerosed, fibrous cortex. (Hematoxylin and eosin. ×180; reduced ⅓.)

On September 1 she had a normal period, but bled for 8 days beginning on September 15. Bleeding started again on October 6, and was accompanied by pain in the left lower quadrant. She was still bleeding per vaginam when hospitalized on October 9. On examination a freely movable and slightly tender orange-sized mass was felt through the left fornix. At laparotomy on October 10 the left ovary was found to be diffusely enlarged to about three times normal size. Its tunica was thick and opaque, grayish-white. A plum-sized cyst was also closely attached to the ovary. The cyst was removed and, since the appearance of the ovary was considered to be typical of sclerocystic disease, about half of it was removed by wedge operation and the remainder closed with running No. 10 chromic catgut. The uterus did not appear remarkable.

Pathologic Description.—Gross: The specimens were: (A) A 2 inch in diameter cyst with a smooth lining and filled with clear fluid. Its wall was 1 to 2.5 mm. thick and fibrous. (B) A wedge of ovary, 3 by 2 by 2 cm., having a thick, opaque, whitish cortex, beneath which were very numerous smoothly lined cysts (0.2-0.7 cm.) filled with clear fluid of thin consistency.

Microscopic: (A) The large cyst was only partially lined by a single layer of flattened epithelium, and was otherwise unremarkable. (B) Sections of the ovarian wedge showed an appearance typical of sclerocystic (Stein-Leventhal) ovary (Fig. 5).

Follow-Up.—The patient's recovery has been uneventful. Her periods have been regular, but of late she has experienced slight twinges of pain in the left lower quadrant, possibly the result of adhesions. She fancies that the growth of hair generally has become somewhat less marked and finer in texture. She has not conceived again, however, though no preventive measures have been taken. At the time of writing the 24 hour 17-ketosteroid excretion is 11.0 mg.

CASE 2.—This 33-year-old, gravida iii, para iii, was hospitalized on Sept. 28, 1956, for investigation of hypertension and irregular menses. She was sthenically built, and there was moderate generalized hirsuties. The blood pressure was 240/120. Urinalysis, urine concentration power, blood urea nitrogen (9 mg. %), 17-ketosteroid excretion (11.2 mg. per 24 hours), and roentgenograms of skull and sella turcica were found to be normal. On a combination of Serpasil and Apresoline her blood pressure was reduced to 190/110, and she was discharged after 3 weeks.

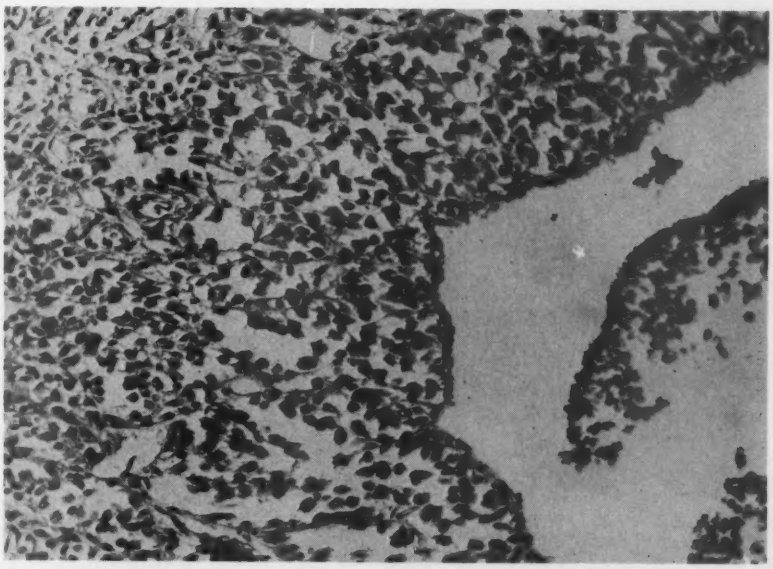


Fig. 6.—Case 2. Follicle cyst. Granulosa (detached during preparation) is unluteinized. Thick, luteinized theca interna. (Hematoxylin and eosin. ×180; reduced ⅓.)

The past history revealed the menarche at the age of 15 years; menses very irregular until she married at 24 years; she thought the overgrowth of hair dated from the menarche. Her pregnancies had not been eventful. Her mother suffered from "high blood pressure," but her 4 brothers and 2 sisters were healthy.

Subsequently she was seen regularly every month at the office. She conceived again in November, 1956, and was hospitalized on May 16, 1957, because of the onset of albuminuria and of puffiness of the face and extremities. The urine showed 4 plus protein, and the blood pressure was 210/140. She was treated as having pre-eclampsia, but she suddenly became unconscious and died on the day following admission to hospital. By postmortem cesarean section a 28 weeks' male fetus was delivered and lived 24 hours.

Autopsy Findings.—Significant findings were cerebral hemorrhage, edema of the lungs, left ventricular hypertrophy, and normal adrenals. Each ovary was slightly and diffusely enlarged (4 by 2½ by 2 cm.), and had a firm, thick, opaque, white cortex, beneath which were many small follicle cysts (up to 0.6 cm.), though not as many as in the typical sclerocystic ovary. Remarkable microscopic findings were benign arteriolonephrosclerosis; a remarkable amount of thymic tissue remaining in a grossly fatty thymus; normal adrenals. The ovaries (Fig. 6) displayed marked sclerosis of the cortices, which contained only a few atretic

and distorted primordial follicles. In the subcortical cysts the granulosa was rarely more than 5 cells thick and was unluteinized. The theca interna layer, however, was 5 to 40 cells thick and markedly luteinized. Broad sheets and columns of luteinized theca cells were seen in the stroma between and beneath the follicle cysts. The corpus luteum of gestation was present in one ovary; it measured 1 cm. in diameter, and its cells were shrunken, ragged, and pale-staining.

CASE 3.—A 32-year-old, white, gravida vi, para v, was first seen in December, 1953, because of severe vomiting. She was then 5 months pregnant, but her sickness had started only a few days before she reported. The past history and previous pregnancies were uneventful. Office examination failed to disclose any abnormality, and conservative home treatment was prescribed. Her condition, however, did not improve and on Jan. 22, 1954, the vomiting became worse, was accompanied by marked nausea and anorexia and severe diffuse abdominal pain. On the next day she complained in addition of headache, marked weakness, and right-sided abdominal pain. Questionable jaundice was noted, and she was hospitalized and treated for acute yellow atrophy.

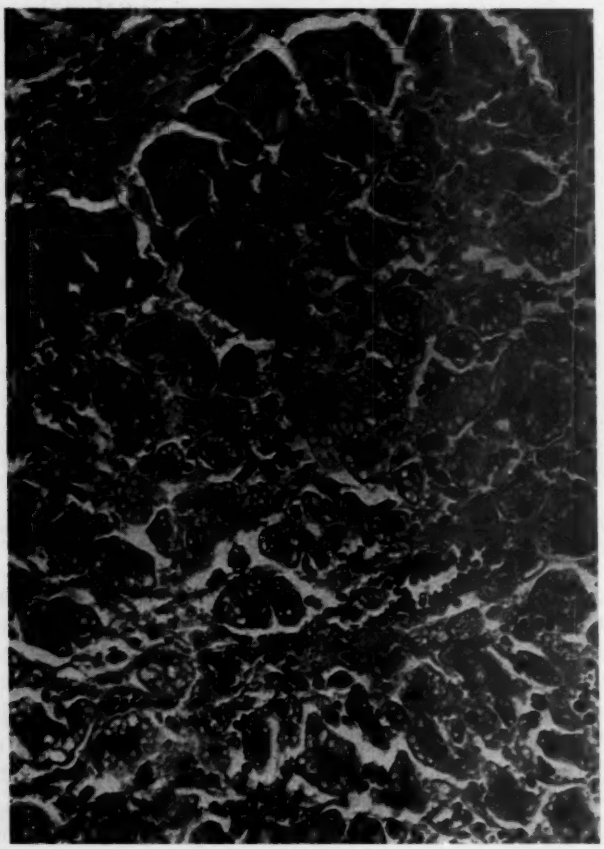


Fig. 7.—Case 3. Liver, showing foamy lipid vacuolation and degeneration of cells of central two thirds of lobule. (Hematoxylin and eosin. ×300; reduced ⅓.)

There had been no infectious illness in her family and no infectious hepatitis in the district. Three days after admission to the hospital she had a spontaneous miscarriage of a stillborn 5 to 6 months' fetus, and almost immediately lapsed into coma, from which she could not be roused during the subsequent 36 hours until her death. Jaundice became obvious and increased, and she developed bleeding from the gums and purpura following skin traumas.

Her breath had an odor of "damp hay." The blood pressure was 140/80. The liver was not palpable and was smaller to percussion than normal. Significant laboratory findings during her 6 days in the hospital were: *Urine:* specific gravity, 1.006-1.010; protein, trace to 1 plus; bilirubin, negative; urobilin, moderately increased; acetone, negative; chlorides, 0.4-0.8 Gm. per liter; terminally there were broad granular casts, and paper chromatography showed marked aminoaciduria, provisionally identified as mainly glutamic acid; no leucine or tyrosine crystals were seen, though looked for. *Blood:* hemaglobin 15.9 Gm. (108%); leukocyte count 6,500-12,900 per cubic millimeter; segmented neutrophils 63-77%; terminally there were 3 normoblasts per 100 white blood cells in the peripheral smears, but tests for hemolysis were

Fig. 8.

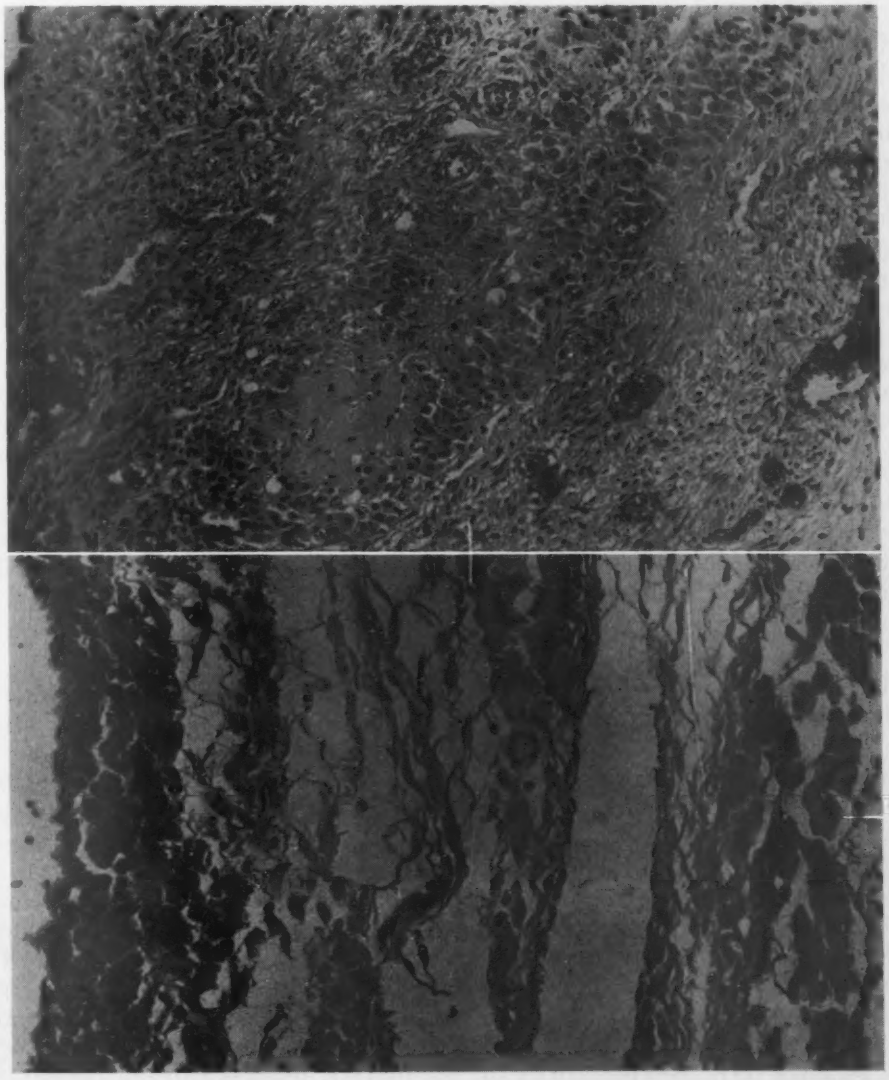


Fig. 9.

Fig. 8.—Case 3. Ovarian cortex somewhat sclerosed. Luteinized theca cells are seen in an old scarred follicle. (Hematoxylin and eosin. ×180; reduced ⅓.)

Fig. 9.—Case 3. Luteinized theca cells in wall of follicle from which granulosa has atrophied (left); also columns of luteinized theca cells in loose stroma. (Hematoxylin and eosin; ×180; reduced ⅓.)

negative, and spectroscopy of plasma was normal; blood nonprotein nitrogen, 27-37 mg. %; blood sugar, 80 mg. %; direct van den Bergh test, positive; serum bilirubin 5.8 mg. %; thymol turbidity, 4.5 units; serum colloidal gold, negative.

Placenta.—The only gross findings were some infarctlike areas and hemorrhage on the maternal aspect. There was no evidence of even partial hydatidiform mole change. Sections showed only considerable hyalinization on the maternal aspect.

Autopsy.—Significant findings were: sthenic build, but no definite signs of virilization; jaundiced. Brain, negative; scattered hemorrhages in edematous lungs. The liver was uniformly shrunken (925 grams) and yellow on capsular and cut surfaces, but the lobular architecture was extant. Petechiae were present in the mucosa of stomach and duodenum. A cortical adenoma 0.75 cm. in diameter was present in the right adrenal. Each ovary was replaced by a large-fist-sized cluster of grapelike cysts filled with slightly cloudy fluid. A corpus luteum was not found.

Microscopic.—In the liver there was acute centrilobular passive congestion of mild degree. In the central one half to two thirds of all lobules the sinusoids were widened and the remaining liver cells filled with tiny fat vacuoles (about the size of red blood cells) (Fig. 7). Many liver cells in this area were shrunken and collapsed and, evidently, many had disappeared altogether. There were minimal inflammatory infiltrate and no significant increase in cells in the portal areas, and no proliferation of bile ducts. The adrenal adenoma consisted of regular trabeculae and alveoli of finely vacuolated cortical cells. The kidneys showed marked cloudy swelling of the epithelium of the convoluted tubules. In the pituitary, which showed the normal hypertrophy associated with pregnancy, the majority of the cells were large, eosinophil "pregnancy" cells. The thymus showed fatty tissue with scattered lymphoid follicles. Sections of marrow, thyroid, breast, spleen, and pancreas were unremarkable. Sections of fetal tissues were normal apart from eosinophilic secretion in diffusely dilated pancreatic acini. On section the ovaries were seen to be very vascular. Despite the cystic nature, the cortices were relatively sclerotic (Fig. 8). The cysts were of follicular type. The granulosa layers were atrophied in most, intact in some, and showed very early luteinization in a few. The striking microscopic feature of the ovaries was the greatly hypertrophied (7 to 25 cells thick) luteinized theca layer in the walls of all cysts, even in old atretic and fibrosed follicles (Fig. 8). Trabeculae and sheets of luteinized theca cells were everywhere seen throughout the loose and edematous stroma (Fig. 9).

Comment

It appears reasonable to conclude that none of these cases represents tumor development on the part of the ovary or any of its cellular elements. Rather must the cases be classified broadly as hyperplasia of the theca cells, i. e., hyperthecosis ovarii, which, in the present state of our knowledge, is better qualified as being idiopathic or of obscure etiology. Case 1 is of particular interest in that in it the question is posed whether this represents pregnancy changes in the Stein-Leventhal syndrome or is better classified as hyperthecosis associated with pregnancy. In this presentation we are following the classification used at the Massachusetts General Hospital and using the term hyperthecosis.[10] In so doing, however, we feel no more secure than the workers there, as the two syndromes appear to overlap considerably, and one cannot help but feel that the difference may be one only of degree. Nevertheless, if we are to take Case 1 as an example of pregnancy-induced changes in a sclerocystic ovary we have then to explain why the sclerocystic process affected (apparently) only one ovary at first. For all that, the wedge removed from the second ovary was typical grossly and microscopically of the Stein-Leventhal syndrome. In Case 1 of Rottino and McGrath[11] one ovary appears to have been of the sclerocystic type, but the other was replaced by a pseudomucinous cystadenoma. We are not aware of any authentic case of unilateral sclerocystic (polycystic) disease.

Our Case 2, we feel, represents a mild degree of sclerocystic ovarian disease in which pregnancy occurred. In adopting this view we are concurring with Shippel's[7] hypothesis that there are grades and stages of the process. The 17-ketosteroid excretion in this case was in the upper levels of normal for our laboratory. This may be of interest in that it is recalled that evidence of adrenal hyperplasia has been adduced in some instances of hyperthecosis.[4, 5, 10, 12] In our Case 2, however, we are unable to satisfy ourselves that there is any histologic evidence of adrenal hyperplasia, though we recognize the personal element in such appraisal. It is also, perhaps, worth remarking in this connection that Cases 1 and 2 showed an unusual degree (in our experience) of thymic tissue for the patients' ages. It is interesting, too, though unjustifiable on the evidence available, to speculate on what if any deleterious effect the hyperthecosis of Case 2 may have exercised on her hypertension. Clearly, we need much more information and observation of the ovaries in various conditions associated with pregnancy.

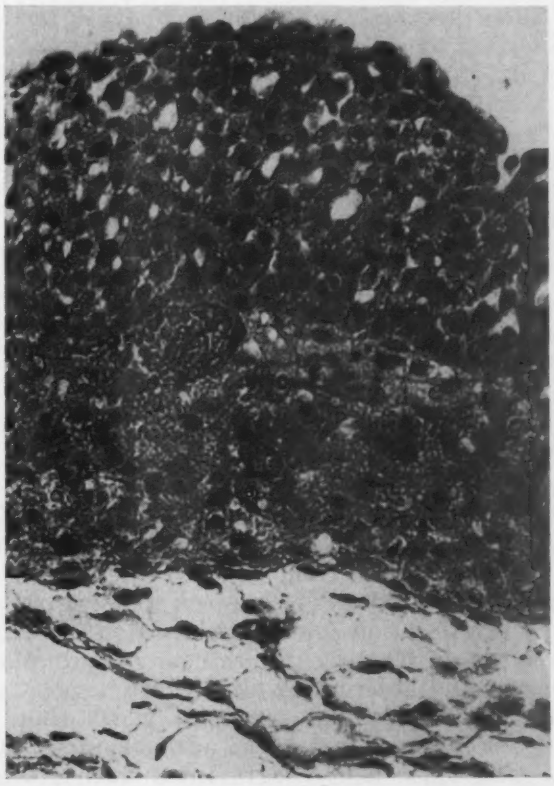


Fig. 10.—Ovary from case of hydatidiform mole. Luteinized granulosa and theca interna layers are well seen. The theca cells are coarser and more granular than in hyperthecosis cases. (Hematoxylin and eosin. ×300; reduced ⅓.)

While our Case 3 shares with the others the common feature of hyperthecosis, there are obvious major dissimilarities. To begin with, the gross appearance of the ovaries in this case was entirely different. Indeed, we have never seen such ovaries except in association with hydatidiform mole and choriocarcinoma. Yet careful examination of the placenta failed to reveal even a vestige of hydatidiform change. Again, despite the gross appearance of the ovaries, sections showed some sclerosis of the cortices (Fig. 8). Does this signify some relationship to the sclerocystic syndrome, and, if so, does this kinship stem

from the great degree of theca cell activity? Comparison with ovaries found in association with hydatidiform mole (Fig. 10) suggests to us that there are subtle differences to be seen in Case 3. In the ovaries of hydatidiform mole there is a moderate degree of luteinization of granulosa to be seen in a goodly proportion of cysts, whereas careful search of dozens of sections from different blocks of Case 3 has failed to reveal any but the faintest suggestion of luteinization of the granulosa cells. In addition we feel that in the cystic ovaries of hydatidiform mole the theca cells are larger and show some vacuolation or foaminess of cytoplasm, which is more granular and definitely less hyaline than in Case 3 (Fig. 10). Finally, there are fewer theca cells in the loose stroma of the ovaries of hydatidiform mole, and these cells take up more fat stain than those in Case 3, where they were virtually negative.

The acute yellow atrophy seen in our third case is of particular interest in itself. We regard this as belonging to the category of "obstetric acute yellow atrophy" described by Sheehan.[13] The clinical course in our case is similar to that described in his 6 cases, and the distinctive pathologic findings in the liver are the same as those described by him and by Ober and LeCompte.[14] The latter authors found that the fat which bloats the cells of the central two thirds of the lobules in a fine foam of vacuoles corresponds closely on analysis to the hepatic lipids in ethionine-treated fasted female rats. Sheehan considered that the liver changes in his cases were probably primary but that they could also represent the result of a particular type of metabolic disturbance. Dow[15] found that stilbestrol dipropionate led to considerable fatty change in the centrilobular two thirds of the hepatic lobules of the adult cat, but the lipid vacuoles in these experimental animals were very much larger than those seen in the syndrome of obstetric acute yellow atrophy. We consider it possible that the liver changes in such cases may be secondary to an unduly high or abnormal output of ovarian hormones. Sheehan made no mention of the ovaries in his 6 cases. Closer study of the ovaries and of the excretion of hormones in cases of obstetric acute yellow atrophy appear to be indicated.

The physiologic function and pathologic significance of the theca cell are far from being clearly understood. Shippel[16] considered the theca cell as the homologue of the testicular Leydig cell and as the source of androgen in the ovary. Indeed, he implied that it may produce a "bisexual androgenic hormone." We find no cause to disagree with this interpretation, and, broadly speaking, in our wedge material from cases of Stein-Leventhal syndrome we have noted (a) a direct relationship between the degree of masculinization and the extent of proliferation and "luteinization" of theca interna cells; (b) an inverse relationship between floridness of granulosa and theca cell layers. If this concept and observation are correct it seems entirely possible to us that cases of the Stein-Leventhal syndrome which show increased urinary excretion of 17-ketosteroids may not be of adrenal origin but due to the proliferation of theca cells which have progressed to such a degree that they add measurably to the output of steroids. In support of this we wish to cite the case of Alexander and Beresford[17] in which masculinization developed during pregnancy in a 24-year-old woman and was due to bilateral huge cystic ovaries, the histologic picture of which was quite similar to that seen in our Case 3. Prior to removal of the cysts the 24 hour output of 17-ketosteroids in the patient described by these authors was 100-104 mg., a figure that fell dramatically after removal of the cysts to 3 mg. Buxton and Van de Wiele,[4] however, found no change in the hormone output in 3 cases of polycystic ovary syndrome studied by column chromatography before and after wedge resection. Nevertheless, they pointed out that, theoretically, if some cases of the Stein-Leventhal syndrome are due to adrenal hyperactivity these cases might be

expected to respond to cortisone, but this was not shown to be the case. The fact that some cases of this syndrome are not benefited by operation does not in our opinion necessarily mean that they are extragenital in origin, since if there is pronounced thecal activity the amount of tissue remaining may be more than enough to perpetuate the syndrome and to preclude breaking the vicious cycle. We heartily agree with Shippel[7] that "... it is most unfortunate that luteinization of a cell has come to be blindly accepted as signifying progesterone activity."

Disturbances in the pituitary-adrenal-ovarian hormone balance have most generally been invoked as the cause of the polycystic ovary syndrome, with the emphasis on the pituitary as the prime offender.[2, 4, 12, 18, 19] Shippel,[7] however, believes that the hyperthecosis condition is not hypophyseal in origin but is due rather to factors inherent in the ovary. There is, nevertheless, a not insignificant body of experimental work favoring a pituitary stimulus.

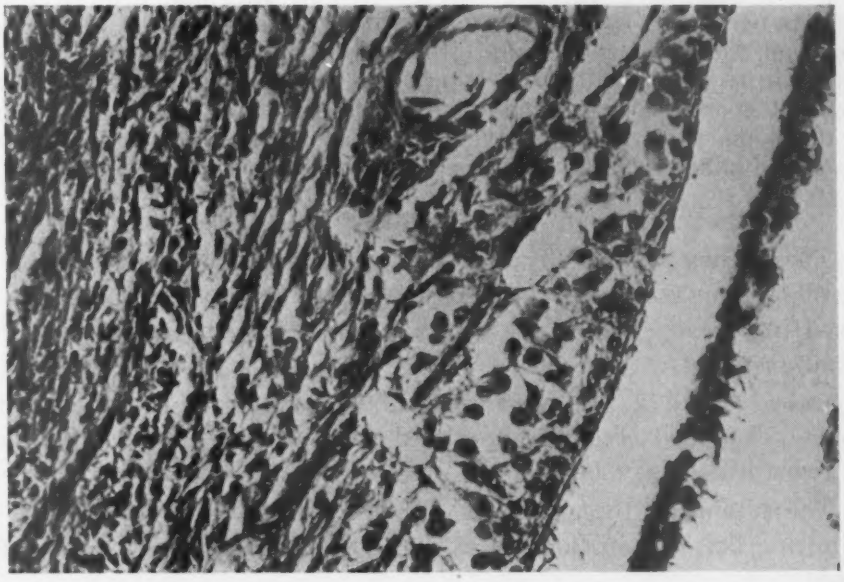


Fig. 11.—Ovary from 18-year-old, 5 months pregnant woman, killed in automobile accident. The theca interna layer is thin and not at all as well "luteinized" as in hyperthecosis cases. (Hematoxylin and eosin. ×300; reduced ⅓.)

Robinson[2] credited Noguchi[20] as being the first to describe experimental luteinization of the theca interna in hypophysectomized rats injected with pregnancy urine. Buxton and Van de Wiele[4] quoted Guyénot and co-workers[21] as showing that injection of chorionic gonadotropins in guinea pigs produces ovarian changes similar to those seen in the human polycystic ovary, and that this is accompanied by unmistakable signs of virilization, an effect that is mediated through the ovary since it fails to develop if the animal has been castrated before the injections. Selye and Collip,[22] by injection of A.P.L. hormones into immature rats and into hypophysectomized rats,[23] produced marked theca-cell luteinization without maturation of follicles. Geist[24] injected 50 women 33 to 48 years of age with 600 to 2,200 R.U. of Antuitrin-S prepared from pregnancy urine over periods of 36 to 100 hours, and noted ovarian congestion, apparent increase in the number of follicles, but arrested follicular development, perifollicular hemorrhages, and some prominence of theca lutein cells. Geist, Gaines, and Salmon[25] produced similar changes in

human ovaries in a study of 91 cases with various gonadotropic hormones, of which hypophyseal members were the most potent. Most of the patients studied by these authors, however, were by nature of the experimental material and conditions somewhat old, and the periods of injections were quite brief.

Our cases here reported may be taken as supporting the pituitary origin of theca-cell hyperplasia and luteinization since they all occurred in the course of pregnancy. It is, of course, well recognized that there is some theca-cell hyperplasia during normal pregnancy, though it is tacitly conceded that this is slight.[24] In the ovaries from normal pregnancies which we have studied we have found theca-cell hyperplasia and luteinization to be of mild degree (Fig. 11) and in no way comparable to the cases under discussion. Does this imply by analogy with Collip and Selye's deductions[22, 23] that the pituitary secretions in these 3 cases were relatively deficient in some factor necessary for the stimulation of the granulosa elements? It may also be asked to what extent is ovarian theca-cell hyperplasia responsible for the masculinizing features of normal pregnancy. To us the striking fact that a large proportion of patients with the Stein-Leventhal syndrome have shown irregularity of menses from the menarche points either to an inborn imbalance of hormone secretions or to abnormality of response on the part of the target organ. To what extent spontaneous pregnancy in such cases will lead to deviations in sexual development of the fetus will be revealed only by careful chromosomal sexing of the offspring in such cases.

Summary

1. Three cases are described, all showing marked hyperplasia and luteinization of ovarian theca cells in association with pregnancy. Virilization was displayed in 2 cases. The course in Case 3 may have been too rapid for this to become manifest.

2. Cases 1 and 2 are considered to be related to the Stein-Leventhal syndrome. The third case was associated with obstetric acute yellow atrophy of the liver, which may be related to the abnormal ovarian hormone output.

3. The luteinized theca interna cell is believed to be the source of the masculinizing hormone in the first 2 cases and also in the sclerocystic ovarian syndrome.

4. The term "luteinization" in regard to theca cells is unfortunate. Adrenal cortical cells might equally be described as "luteinized."

The biochemical investigations were carried out by Mr. L. D. Mellor, F.I.M.L.T., S.T., R.T. The sections were prepared by Mrs. I. B. Eley, S.T., R.T.

References

1. Stein, I. F., and Leventhal, M. L.: Am. J. Obst. & Gynec. 29: 181, 1935.
2. Robinson, M. R.: Am. J. Obst. & Gynec. 30: 18, 1935.
3. Stein, I. F., Cohen, M. R., and Elson, R.: Am. J. Obst. & Gynec. 58: 267, 1949.
4. Buxton, C. L., and Van de Wiele, R. L.: New England J. Med. 251: 293, 1954.
5. Haas, R. L., and Riley, G. M.: Obst. & Gynec. 5: 657, 1955.
6. Culiner, A., and Shippel, S.: J. Obst. & Gynaec. Brit. Emp. 56: 439, 1949.
7. Shippel, S.: J. Obst. & Gynaec. Brit. Emp. 62: 321, 1955.
8. Novak, E.: Personal communication re Case 3.
9. Lillie, R. D.: Histopathologic Technic and Practical Histochemistry, ed. 2, Philadelphia & Toronto, 1954, Blakiston Company.
10. Case Records of Massachusetts Gen. Hosp.: New England J. Med. 257: 1086, 1957.
11. Rottino, A., and McGrath, J. F.: Am. J. Obst. & Gynec. 45: 863, 1943.
12. Geist, S. H., and Gaines, J. A.: Am. J. Obst. & Gynec. 43: 975, 1942.

13. Sheehan, H. L.: J. Obst. & Gynaec. Brit. Emp. **47**: 49, 1940.
14. Ober, W. B., and LeCompte, P. M.: Am. J. Med. **19**: 743, 1955.
15. Dow, C.: J. Path. & Bact. **75**: 151, 1958.
16. Shippel, S.: J. Obst. & Gynaec. Brit. Emp. **57**: 362, 1950.
17. Alexander, W. S., and Beresford, O. D.: J. Obst. & Gynaec. Brit. Emp. **60**: 252, 1953.
18. Bailey, K. V.: J. Obst. & Gynaec. Brit. Emp. **44**: 637, 1937.
19. Ingersoll, F. M., and McDermott, W. V., Jr.: AM. J. OBST. & GYNEC. **60**: 117, 1950.
20. Noguchi, Ko.: Quoted by Robinson.[2]
21. Guyénot, E., Ponse, K., Dottrens, E., Valette, M., and Trolliet, J.: Quoted by Buxton and Van de Wiele.[4]
22. Selye, H., and Collip, J. B.: Proc. Soc. Exper. Biol. & Med. **30**: 647, 1933.
23. Collip, J. B., Selye, H., and Thomson, D. L.: Nature **131**: 56, 1933.
24. Geist, S. H.: AM. J. OBST. & GYNEC. **26**: 588, 1933.
25. Geist, S. H., Gaines, J. A., and Salmon, U. J.: AM. J. OBST. & GYNEC. **42**: 619, 1941.

SERUM LACTIC DEHYDROGENASE ACTIVITY DURING PREGNANCY AND IN THE NEWBORN*

D. D. HAGERMAN, M.D., AND F. M. WELLINGTON, B.A., BOSTON, MASS.

(From the Department of Biological Chemistry, Harvard Medical School, and the Research Laboratories of the Boston Lying-in Hospital)

THE observation that the activity of an enzyme in human serum, transaminase, is markedly increased following acute myocardial occlusion has resulted in a renewed interest in the enzymatic activities of serum. Wróblewski and LaDue[1] and subsequently Wacker and associates[2] have shown that serum lactic acid dehydrogenase activity also increases following myocardial occlusion. Hsieh and Blumenthal[3] described other disease states in which the activity of this serum enzyme was increased. Hanson and Biörck[4] have reported a comparison of various serum enzyme activities with other parameters which might be of value in the diagnosis of myocardial infarction, from which they concluded that determination of serum lactic dehydrogenase activity was inferior for diagnostic purposes to measurement of transaminase activity. Wróblewski, Ruegsegger, and LaDue[5] concluded from experiments in dogs that the elevation of serum dehydrogenase activity resulted from a simple release of the enzyme from injured or dying cardiac muscle. Recently Wróblewski[6] has summarized the present state of knowledge concerning the activity and variations in activity of this enzyme in several body fluids (serum, effusions, and cerebrospinal fluid) under various conditions.

Methods

Peripheral venous or umbilical cord blood was obtained without regard to the fasting state, was allowed to clot at room temperature, and was then immediately centrifuged for separation of the serum. The serum was stored in the cold room at 3° C. until the analysis was made, which was usually on the same day and always within 48 hours of the time of collection of the blood. Since erythrocytes contain the enzyme it is necessary to avoid hemolysis of the blood during collection and separation. Determinations of enzyme activity were made in a Beckman Model DU ultraviolet spectrophotometer exactly as described by Wacker and co-workers, except that in the interest of economy the amount of diphosphopyridine nucleotide used was reduced from 5×10^{-3} molar (0.3 ml. of a 0.05 molar solution) to 7.5×10^{-4} molar (0.3 ml. of a 0.0075 molar solution). (The diphosphopyridine nucleotide Michaelis constant, K_M, for crystalline muscle lactic acid dehydrogenase is given by Kubowitz and Ott[7] as 5×10^{-6} molar). Enzyme activity is reported in the usual

*This investigation was supported by grants from the Charles A. King and Marjorie King Fund and by research grant C2400 from the National Institutes of Health, United States Public Health Service.

units, one unit being the enzyme activity which will cause an increase in optical density at 340 mμ of 0.001 per minute per milliliter of serum during the early, linear portion of the reaction. Analyses were made in duplicate on each serum sample.

Results

Determinations of enzyme activity in a small group of healthy males gave a value of 110 ± 12 (mean ± standard deviation) units, while samples from a group of healthy, nonpregnant females gave a value of 103 ± 27 units. These values are inexplicably about 80 per cent higher than the normal values reported by Wacker and his associates but as indicated by the magnitude of the standard deviation and by the reproducibility of the assay on replicate samples of the same serum the difference is probably not the result of a sampling error. Reduction of the amount of diphosphopyridine nucleotide used would slow the reaction so that this modification of the method does not account for the observed difference.

The variation between subjects, as measured by the standard deviation, is about twice as great in the females as in the males and comparison of the individual values for the females with the stage of their menstrual cycles suggested a correlation between these variables. The experiment whose results are given in Fig. 1 was therefore done. Each point in the graph is the result of a duplicate determination of serum lactic dehydrogenase activity in the same healthy woman (age 25 years) on different days of her menstrual cycle. It is clear that there is a cyclic variation of serum enzyme activity with the menstrual cycle, with a minimum near the mid-point of the cycle.

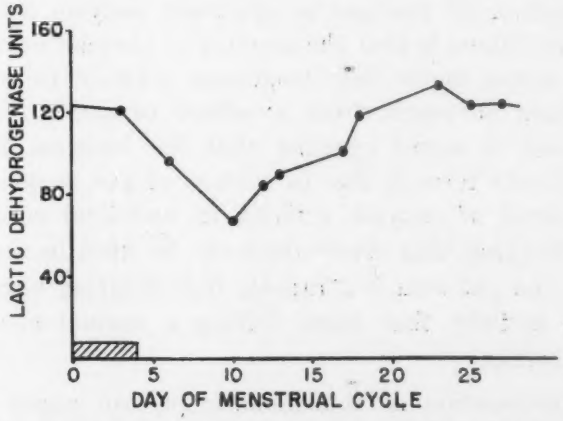


Fig. 1.—Variation of serum lactic acid dehydrogenase activity with the menstrual cycle in a young healthy woman.

During pregnancy activity of the enzyme remains near the normal level until the last 6 weeks of gestation (Table I). Then a steady increase begins until at term about 50 per cent more than the normal lactic dehydrogenase activity is present in the serum. Analysis of variance of the data of Table I shows that the means given are significantly different at the 99 per cent confidence level. The values in Table I for the thirty-ninth and fortieth weeks of gestation were all obtained before labor had begun. Table II gives the results of determinations done during labor. Early in labor the serum enzyme activity has apparently decreased to the "normal" value but as labor proceeds it again rises and remains high for at least 2 hours after delivery. Serial determinations were made on some of these patients and these results

were consistent with the averages given in the table. Table II also includes values for umbilical cord blood obtained immediately after delivery of the placenta.

TABLE I. SERUM LACTIC ACID DEHYDROGENASE ACTIVITY IN THE THIRD TRIMESTER OF PREGNANCY

	GESTATIONAL AGE IN WEEKS					
	29-30	31-32	33-34	35-36	37-38	39-Term
Units enzyme activity ± standard deviation	114 ±32	93 ±16	100 ±23	120 ±20	149 ±32	155 ±25

TABLE II. SERUM LACTIC ACID DEHYDROGENASE ACTIVITY DURING AND AFTER LABOR, AND IN UMBILICAL CORD BLOOD

	TIME AT WHICH BLOOD WAS TAKEN				
	EARLY LABOR	MID-LABOR	AT TIME OF DELIVERY	2 HOURS AFTER DELIVERY	UMBILICAL CORD BLOOD
Units enzyme activity ± standard deviation	106 ±22	116 ±22	132 ±23	153 ±20	218 ±49

Comment

Although the activity of an enzyme is acutely sensitive to the conditions present in the environment in which it is acting (pH, salt concentration, presence of activating or inhibiting ions, substrate concentration, etc.), the simplest interpretation of changes in apparent enzyme activity determined under standard conditions is that the amount of enzyme present has changed. The increase in serum lactic dehydrogenase activity following myocardial infarction is thought to result from a release of the enzyme from injured cardiac muscle, and it seems possible that the increase in serum enzyme activity observed near term is due to release of the enzyme from placental cells. The high level of enzyme activity in umbilical cord blood supports this conclusion. Perhaps this observation can be used in support of the concept that at term the placenta is a rapidly deteriorating organ. The changes in serum enzyme activity that occur during a normal menstrual cycle are more difficult to explain.

During the preparation of this manuscript, the paper of Knutson and co-workers[8] appeared. These authors refer to earlier reports in which both elevation and no elevation in serum lactic dehydrogenase activity were found during pregnancy, and describe the results of their own experiments in which no difference in the activity of this enzyme was found between pregnant and nonpregnant women. The reasons for these discrepancies in the literature are not at all clear, and indicate a need for further careful experimentation.

Summary

1. In the nonpregnant woman serum lactic acid dehydrogenase activity undergoes cyclic variations which are correlated with the stage of the menstrual cycle.

2. During the last 6 weeks of pregnancy there is a striking rise in the activity of this enzyme in the serum which is possibly due to its release from degenerating placental cells.

We are indebted to the house staff of the Boston Lying-in Hospital and particularly to Dr. Philip Corfman for aid in obtaining the blood samples.

References

1. Wróblewski, F., and LaDue, J.: Proc. Soc. Exper. Biol. & Med. **90**: 210, 1955.
2. Wacker, W. E. C., Ulmer, D. D., and Vallee, B. L.: New England J. Med. **225**: 449, 1956.
3. Hsieh, K. M., and Blumenthal, H. T.: Proc. Soc. Exper. Biol. & Med. **91**: 926, 1956.
4. Hanson, A., and Biörck, G.: Acta med. scandinav. **157**: 493, 1957.
5. Wróblewski, F., Ruegsegger, P., and LaDue, J. S.: Science **123**: 1122, 1956.
6. Wróblewski, F.: Am. J. M. Sc. **234**: 301, 1957.
7. Kubowitz, F., and Ott, P.: Biochem. Ztschr. **314**: 94, 1943.
8. Knutson, R. G., Cornatzer, W. E., Moore, J. H., and Nelson, W. W.: J. Lab. & Clin. Med. **51**: 773, 1958.

ECTOPIC PREGNANCY: A REVIEW OF FIFTY CASES AT TRIPLER U. S. ARMY HOSPITAL

F. L. Soisson, Captain, USAF (MC), and
J. P. Moran, Captain (MC) USN

(From the Obstetrical-Gynecological Service, Tripler U. S. Army Hospital)

ECTOPIC pregnancy is both an interesting and a challenging problem. The literature on the subject is voluminous and the problem has been approached from many angles. Much has been done to bring about a favorable outcome through better anesthesia, the availability of blood banks, and improvements in surgery. Fifty consecutive cases of ectopic pregnancy, 48 tubal and 2 ovarian, observed at Tripler U. S. Army Hospital during the years 1956 and 1957 are presented. An attempt is made to correlate the several diagnostic procedures with accuracy in reaching the diagnosis and to emphasize the pitfalls along the way to correct definitive treatment. It is felt that an analysis of all patients in whom the diagnosis was entertained at initial examination and of all patients in whom the diagnosis was not suspected but proved after further observation is of value. These cases all occurred in dependents of military personnel and were handled completely by the resident and teaching staff of a large military hospital.

Definition

Ectopic pregnancy is, by definition, any pregnancy which occurs outside the uterine cavity where implantation of a fertilized ovum would ordinarily take place. This includes a pregnancy in the uterine cornu, the cervix, the Fallopian tube, or outside the Fallopian tube in the abdominal cavity, the ovary, or the cul-de-sac. The most common site for an ectopic pregnancy is in the Fallopian tube, consequently ectopic pregnancy is usually associated with or thought of as a tubal pregnancy.

In this series, there were 48 tubal pregnancies and 2 pregnancies in the ovary, all of which were proved by histologic examination. The 2 ovarian pregnancies, however, did not fulfill the criteria set forth by Spiegelberg.[18] In each instance both tubes appeared normal at the time of laparotomy and were not removed. The etiology of the bleeding was felt to be a ruptured corpus luteum cyst which was resected. Both of the surgical specimens, however, at the time of histologic examination were found to contain trophoblastic villi within the substance of the ovary.

Statistical Data

Both the outpatient and inpatient charts of this series of 50 patients were thoroughly reviewed. All important statistical data were then tabulated.

Table I is an analysis of the number of patients in whom the diagnosis of ectopic pregnancy was made at the time of the initial visit to this hospital, as well as the number of patients who were seen previously at either this hospital or an outside dispensary. It was felt necessary to separate previous visits to our own Gynecology Clinic from dispensary visits because of the difference in personnel as well as the availability of diagnostic procedures. Four patients had incomplete records regarding previous gynecologic visits. Thirty cases were diagnosed at the time of the initial visit to the hospital. Ten patients had been seen at least once previously in the Gynecology Clinic before admission to the hospital. There was one case of unsuspected ectopic pregnancy which was found at the time of a bilateral salpingectomy and total abdominal hysterectomy for chronic pelvic inflammatory disease.

TABLE I. OBSERVATION PERIOD

	NO.	%
Diagnosis made on initial visit to hospital	30	60
Patients previously seen in dispensary—sent home	3	6
Patients previously seen in Outpatient Clinic here—sent home	2	4
Patients previously seen in Gynecology Clinic here—sent home	9	18
Four previous visits to Gynecology Clinic here	1	2
No record of previous examinations	4	8
Unsuspected ectopic pregnancy—incidental finding at laparotomy for pelvic inflammatory disease	1	2

TABLE II. INCIDENCE

	1956	1957	TOTAL
Major surgical procedures done on Gynecology Service	173	239	412
Ectopic pregnancy suspected, laparotomy performed	31	39	70
Proved ectopic pregnancy at laparotomy	20	30	50
Abortions at this hospital	366	329	695
Deliveries at this hospital	4,454	3,391	7,845
Incidence/total pregnancies	1/242	1/125	1/172
Incidence/total deliveries	1/223.7	1/113	1/176.8
Correct preoperative diagnosis	20/31—64.5%	30/39—77%	50/70—70%

Incidence.—The number of ectopic pregnancies at this hospital varied considerably over the 2 year period reported. Although Table II indicates a remarkable increase in the incidence of ectopic pregnancy, this is not entirely true. In 1957, because of participation in Medicare, the delivery rate at this hospital decreased 25 per cent with no appreciable change in gynecologic admissions. Also, many of these patients were seen under emergency conditions and therefore did not seek civilian medical care. The number of ectopic pregnancies gradually increased over this period of time while the delivery rate was decreasing, thereby markedly increasing the percentage of ectopic pregnancies. The over-all incidence was one ectopic pregnancy for 176.8 deliveries. Although the incidence of ectopic pregnancy is usually recorded as the number of ectopic pregnancies occurring in relation to term deliveries, an attempt was also made from this study to report the incidence of ectopic pregnancy in relation to total pregnancies. In the literature, the

incidence of tubal pregnancy has varied according to the author reporting and the number of cases in his series. Both Eastman[9] and Novak[16] reported that tubal pregnancy occurs approximately once in 250 deliveries. Other authors have reported the incidence as one in 60,[7] one in 49,[13] one in 99,[17] one in 139,[3] and one in 264[15] deliveries.

Age.—Forty per cent of the patients from this series were under the age of 25 and an additional 26 per cent under the age of 30. This is to be expected in view of the fact that patients who are treated at this hospital are of an early childbearing age. The average age of the entire group was 27.8 years which is in agreement with the data of both Kohl[13] and Ware and Winston.[20]

Race.—From this series, 39 patients were Caucasians, 1 Negro, 7 were Orientals, and 3 Malayan. Because of the large percentage of both Oriental and Malayan dependents seen at this hospital, one would expect the last two figures. There was only one Negro patient in the entire series. It has been generally accepted that the incidence of ectopic pregnancy is somewhat higher in the Negro population in comparison to whites. The racial incidence again has varied according to the author reporting; 1 in 215 deliveries among white patients as compared to 1 in 96 among Negro patients according to Fontanilla and Anderson[11] from the Baltimore area, 1 in 160.6 deliveries for whites as compared to 1 in 93.2 deliveries for Negroes according to Word.[21]

Gravidity.—The higher the gravidity, the less one encounters ectopic pregnancy. Fifty-six per cent or over half of the patients in this series were unfortunate in having either their first or second pregnancy occur outside the uterine cavity. The percentages in Table III are fairly consistent with similar and larger ectopic pregnancy series.[10, 20]

TABLE III. GRAVIDITY

GRAVIDITY	NO.	%
0	10	20
1	18	36
2	7	14
3	8	16
4 or more	7	14
Total	50	100

Etiology

Ectopic pregnancy has long been suspected to be due to one or more of several factors. Novak[16] conveniently divided these into two main groups, (1) factors which delay or prevent the passage of the fertilized egg into the uterine cavity, and (2) factors which increase the receptiveness of the tubal mucosa to the fertilized egg. The greatest number of causes fall under the first group, while the second group is less clearly demonstrable, though of definite importance. Just what degree of importance is to be attributed to this factor of individual tubal receptiveness to implantation is still a matter of dispute. It is generally agreed that organic changes in the uterine tubes resulting from either congenital malformations or previous inflammation stand out as the foremost causes of this particular condition.[2] Today, many inflammatory processes are felt to be implicated. Whereas originally gonorrheal salpingitis was thought to be the main offender, we must also consider salpingitis secondary to postdelivery or postabortal inflammation, following dilatation and curettement, and also genital tuberculosis.[12] Other factors such as infantile tubes, mechanical obstruction secondary to adhesions from previous laparotomies, endometriosis of the tube, and improperly functioning tubes

from previous ectopic pregnancies or plastic procedures all must be considered. Table IV shows several possible causes of ectopic pregnancy which were considered in this study. In only 14 per cent of cases could a definite history of previous pelvic inflammatory disease be obtained. Many patients had a problem of infertility for 3 or more years. There were only 2 cases of previous ectopic pregnancy and in only a very few cases was there any history of possible pelvic infection following delivery. Previous laparotomy, previous dilatation and curettage, and previous abortion play a part in this problem. In one case the patient stated that she had had a previous tubal resection for pelvic inflammatory disease. At the time of operation the tube in which the ectopic pregnancy occurred had ruptured, while on the opposite side there was a definite defect in the tube compatible with a tubal resection. As stated above, previous pelvic inflammatory disease was always felt to be a big factor in the etiology of tubal pregnancy, a fact that was thought to be substantiated by the higher incidence of ectopic pregnancy in the Negro race. There also seems to be a high incidence of ectopic pregnancy in the Oriental group, possibly for the same reason, as well as a high incidence of tuberculosis of the genital tract. Within the last few years, we have had to face what appears to be a slow but steady increase in the number of ectopic pregnancies. A second but new factor which has been implicated is the use of antibiotics in treatment of pelvic inflammatory disease. A reasonable explanation offered by most authors is that the tube which originally was occluded by the normal process of infection is now only partially closed, scarred, and without normal peristalsis as a result of treatment with antibiotics. The predominant cause of ectopic pregnancy, however, is abnormal tubal physiology which is probably due to one or more of the afore-mentioned factors.

TABLE IV. ETIOLOGY IN 50 CASES

ETIOLOGY	1956	1957	TOTAL	%
Infertility (3+ years)	4	4	8	16
Previous dilatation and curettage	2	5	7	14
Previous laparotomy	1	11	12	24
Previous ectopic pregnancy	0	2	2	4
Pelvic inflammatory disease	2	5	7	14
Previous abortion	5	8	13	26

Symptoms

The diagnosis of ectopic pregnancy depends a great deal on the history and physical examination. There were three outstanding signs or symptoms present in the history of these patients: (1) abdominal pain, (2) a history of vaginal bleeding either before or at the time of admission, and (3) a period of amenorrhea. Forty-nine patients had as their chief complaint abdominal pain, either generalized or localized. The only other patient was admitted for an elective laparotomy for pelvic inflammatory disease and was found to have an incidental ectopic pregnancy as well. A history of vaginal spotting either prior to or at the time of admission was significant. Forty-five patients had a period of amenorrhea exceeding 4 weeks and in most cases some form of abnormal menstrual history.

The abdominal pain in most cases was rather severe. Although most patients complained of generalized lower abdominal pain, 28 could localize the pain to either the right or left lower quadrant.

Of the 38 patients with vaginal bleeding, only 15 were found to have bleeding on admission while 22 patients had had vaginal bleeding one or more times prior to admission. In most cases this bleeding was described as small in amount, definitely different from that of a normal menstrual period.

A history of amenorrhea was present in 90 per cent of this series. There were only 5 patients who did not have a period of amenorrhea of at least 4 weeks. The average length of amenorrhea in the entire series was 6 weeks.

TABLE V. SYMPTOMS

SYMPTOMS	TOTAL	%
Abdominal pain	49	98
Vaginal bleeding	38	76
Amenorrhea (4 weeks +)	45	90
Anorexia and nausea	31	62
Dizziness or syncope	25	50
Feeling of defecation	16	32
Shoulder pain	11	22
Vomiting	14	28
Urgency and frequency	8	16
History of pelvic inflammatory disease*	7	14
Infertility (3+ years)	8	16

*One case of recurrent pelvic inflammatory disease with an unsuspected ectopic.

Table V lists the various other symptoms of lesser frequency which were felt to be significant in the history of these patients. Half of them complained of dizziness or syncope due to excess bleeding. Thirty-one patients complained of anorexia and nausea although only half gave a history of having vomited. Other symptoms of peritoneal irritation such as shoulder pain, urgency and frequency, rectal urgency, or a feeling of defecation were present in many of the patients. The classical symptom complex of amenorrhea, vaginal bleeding, and abdominal pain was very significant in this series.

Physical Findings

All patients in this series, except the one with the incidental ectopic pregnancy, were found to have abdominal tenderness on physical examination. Thirty-seven patients had definite rebound tenderness indicative of peritoneal irritation. Associated with the rebound tenderness but to a lesser degree were the findings of abdominal rigidity and abdominal distention. As expected, the pelvic findings were most significant. The cervix was visualized in all patients. Over half had a postive Chadwick's or Hegar's sign and an equal percentage had a tender uterus especially on motion of the cervix. Only 15 patients had a definitely enlarged uterus which might lead one to suspect an intrauterine pregnancy rather than an ectopic gestation. On bimanual examination, however, two thirds of the patients had a definite palpable adnexal mass, tenderness of the cul-de-sac, or cul-de-sac fullness. One or more of these three findings are significant in making the diagnosis of ectopic pregnancy.

TABLE VI. PHYSICAL FINDINGS

PHYSICAL FINDINGS	TOTAL	%
Abdominal tenderness	49	98
Rebound tenderness	37	74
Adnexal mass	32	64
Cul-de-sac fullness	29	58
Cul-de-sac tenderness	33	66
Positive Chadwick or Hegar	27	54
Shock	10	20
Paleness	21	42
Abdominal rigidity or spasm	12	24
Abdominal distention	9	18
Enlarged uterus	15	30
Tender uterus	28	56

Shock or impending shock (rapid pulse and pallor) was found relatively infrequently in this series. Only 10 patients presented with clinical shock while an additional 21 patients were found to be quite pale from blood loss, either acute or chronic. This was a little unusual in view of the fact that 74 per cent of the patients were found at the time of operation to have a ruptured tubal pregnancy. The average blood loss for this series was likewise approximately 700 c.c. per patient (Table VI).

Laboratory

The laboratory studies in most cases were not significant. A complete blood count was done on all patients as part of their routine admission. The hematocrit or hemoglobin was of some value in establishing a base line hemogram but in many cases because of the recent and/or extensive hemorrhage it was not a true value. Any patient who was observed longer than 24 hours had serial hematocrits in an attempt to rule out continued internal bleeding. There were 11 who had an initial hematocrit below 30 which is an indication in our department for an immediate transfusion. Fourteen patients had a hematocrit ranging between 31 and 35 indicative of anemia, while 25 patients had a hematocrit above 35.

The only other test considered to be of some significance in making this diagnosis was the white blood count. It is felt by many authors that elevation in white blood count is characteristic of an ectopic pregnancy, because of the fact that hemorrhage into the peritoneal cavity will usually give a rapid increase in the count with an equally rapid return to normal when the bleeding has stopped. There were 9 patients with a count below 10,000, 23 patients ranging between 10,000 and 15,000, and 18 patients with a count above 15,000.

Diagnosis

A classical case of tubal pregnancy with rupture can be recognized from history and physical examination. The diagnosis of ectopic pregnancy prior to rupture, however, is often extremely difficult and fraught with many errors. When a patient presents sufficient evidence to suggest ectopic pregnancy, there are several diagnostic tests which may be performed to confirm the diagnosis.

TABLE VII. DIAGNOSTIC PROCEDURE

TYPE	1956	1957	TOTAL
Examination under anesthesia	1	2	3
Frog test positive/done	0/7	2/4	2/11
Colpotomy	0	4	4
Culdocentesis, ratio of positive results to no. done	3/3	15/18	18/21
Total, ratio of positive results to no. done	4/11	23/28	27/39

This series involves a 2 year study. During 1956, relatively few such procedures were used (Table VII). There were 31 patients suspected of ectopic pregnancy subjected to laparotomy. Twenty patients, or 64.5 per cent, had proved tubal pregnancy. During 1957 interest in culdocentesis and colpotomy was developed and these procedures were used more freely. Colpotomy was performed approximately 25 times, culdocentesis 30 times, and culdoscopy twice during the year. There were 39 ectopic suspects, 30 of whom (77 per cent) had a proved diagnosis; 28 tubal and 2 ovarian pregnancies. Of the 9 remaining cases, several had a positive cul-de-sac aspiration which was followed by laparotomy. Seven patients had a ruptured corpus luteum cyst

with hemoperitoneum and in 2 no evident pathology was found. In this 2 year period, 70 patients were subjected to laparotomy, 50 of whom had ectopic pregnancies, a correct preoperative diagnosis of 70 per cent.

Pregnancy Tests.—There were 11 patients in this series in whom a pregnancy test was done prior to or at the time of their admission. There were only 2 patients who had a positive result. In both cases pregnancy tests were done at least a week prior to admission to the hospital. One patient was seen in our clinic for approximately 6 weeks during which time she was seen by four different examiners. She had had a positive frog test and was felt to have a bicornuate uterus with the pregnancy in one horn. During this period of time, a second frog test was reported as negative and the uterus did not change in size and she was therefore subjected to an exploratory laparotomy and an interstitial pregnancy was found. A positive test simply means that the chorionic villi are still actively in contact with the maternal blood stream. The pregnancy test in most cases is negative because once the tube has ruptured or the pregnancy has been aborted within the tube, the villi cease to function.

Culdocentesis.—This diagnostic procedure is probably the most simple to perform. Today, many centers use it routinely as a valuable aid in making this diagnosis.[3, 7, 21] One simply needs to insert a long needle into the cul-de-sac through the posterior vagina in order to determine the presence or absence of free blood in the peritoneal cavity. This procedure can be performed in an office, clinic, admitting room, or examining room, and is most useful because of its simplicity. During the second year of this study, there were 18 culdocenteses performed in the 30 cases of proved ectopic pregnancy; 15 (83 per cent) were positive and 3 were negative. One of the patients with a negative cul-de-sac aspiration had an adnexal mass, therefore a colpotomy was performed to verify the diagnosis. The other 2 patients with a negative aspiration were later subjected to a laparotomy when both patients went into shock. In all 3 cases, the operator probably had not penetrated the cul-de-sac. At no time did a cul-de-sac aspiration result in any ill consequences such as perforation of the rectum or peritonitis. A needle aspiration where absolutely no fluid of any kind is obtained should be disregarded, whereas a positive tap (free unclotted blood) should be regarded as positive evidence of intraperitoneal bleeding and followed by a laparotomy.[7]

Colpotomy.—Although only 4 patients from this series underwent colpotomy, there were 21 additional colpotomies performed during the year on patients who presented problems of differential diagnosis. In most cases the possibility of ectopic pregnancy was ruled out, thereby eliminating a needless laparotomy. A colpotomy incision is a simple and safe procedure for the diagnosis of ectopic pregnancy, and frequently the incision is sufficient to allow ample space for removal of the pregnancy.[8] The routine use of the posterior colpotomy incision is advocated by Caldwell,[5] Parker,[17] and Lucci.[15] In none of the patients in whom the diagnosis of ectopic pregnancy was made through a colpotomy incision was the pregnancy removed vaginally. Since all patients were already under general anesthesia at the time of their colpotomy, and because in all cases there was active bleeding, their pregnancies were removed through an abdominal incision. The colpotomy incision is a safe and useful procedure for the diagnosis of ectopic pregnancy but should not be used routinely as a means of removing the pregnancy.

Culdoscopy.—This, too, is a diagnostic procedure which can be of great use in the hands of those skilled in its performance. A culdoscopy clinic was established on the Gynecology Service during December, 1957. Only 2 of

these procedures were performed during the period of this report. In one, suspected ectopic pregnancy was ruled out. Patients have to be somewhat selected for this procedure because of the area involved and its relative uselessness in the face of gross bleeding.[21]

Management

The treatment of ectopic pregnancy is surgical. Excision of the affected tube or pregnancy site with preservation of as much functioning tissue as possible, especially the ovary, is important. This is usually an emergency procedure and should be performed as quickly as possible and without additional elective surgery. In the face of gross bleeding, it is poor technique to undertake appendectomies or removal of an infected salpinx from the opposite side for fear of peritoneal spill in the face of an excellent culture medium. Once the diagnosis of ectopic pregnancy is made, or there is a strong suspicion of it, the surgical treatment should be carried out through a laparotomy incision. As stated before, a correct preoperative diagnosis was made in 70 per cent of the cases reported. Once the diagnosis of ectopic pregnancy has been made, speed in preparation of the patient is essential. In this series, 15 patients were operated upon within 2 hours of admission to the hospital, 14 within 2 to 4 hours of admission, and an additional 10 within 4 to 24 hours of admission (Table VIII). Thus, 78 per cent of the patients were subjected to operation within the first 24 hours of admission. There were 11 patients operated upon from 24 to 72 hours following admission. Seven of these cases occurred during 1956. We feel that had a diagnostic procedure been done earlier in the patient's observation period, this time lag could have been eliminated. Of these 11 patients, 4 had ruptured tubal pregnancies, 2 unruptured tubal pregnancies, and one an unsuspected ectopic pregnancy found at the time of bilateral salpingectomy for chronic pelvic inflammatory disease. In 1957 there were only 4 patients whose observation period exceeded 24 hours. Two of these patients had ruptured tubal pregnancies which were secondarily implanted on the ovary and 2 were unruptured pregnancies. There were 2 patients with ovarian pregnancies in 1957, both of whom had a sudden onset of symptoms and both were operated upon within 4 hours of admission.

TABLE VIII. TIME OBSERVED

TIME	1956	1957	TOTAL	%
Less than 2 hours	6	9	15	30
2-4 hours	3	11	14	28
4-24 hours	4	6	10	20
More than 24 hours	7	4	11	22

We feel that transfusion is second only to operation in reducing maternal morbidity and mortality. After a study of the charts of all patients in this series, the calculated average blood loss was found to be approximately 650 to 700 c.c. (Table IX). Blood transfusions were accurately recorded in all cases and the average blood replacement for the entire series was 850-900 c.c. Thirty patients, or well over half of the series, required at least 500-1,000 c.c. of blood. Twenty-six patients, or over 50 per cent, received 1,000 c.c. or more of whole blood. Blood was given in all cases by the intravenous route. In many cases this was given at a rapid rate under pressure. In none of the cases was it felt necessary to give intra-arterial transfusion. Of the 8 patients who required no blood replacement, 3 had unruptured tubal pregnancies, 3 underwent operation within 4 hours of admission and were felt to have less than

500 c.c. of blood in the abdominal cavity, one was taken to the operating room within 24 hours of admission and was found to have a well-confined rupture within the broad ligament, and one patient was operated on during the third hospital day and was found to have a well-localized but ruptured tubal pregnancy. All patients who were clinically in shock or had very low hematocrits were started on blood replacement prior to anesthesia. In nearly all cases blood replacement was given during the operative procedure.

TABLE IX. BLOOD LOSS AND REPLACEMENT

YEAR	AVERAGE LOSS	AVERAGE REPLACEMENT	NO. OF UNITS PINTS RECEIVED					
			0	1	2	3	4	5
1956	700 c.c.	900 c.c.	4	7	4	1	1	3
1957	680 c.c.	850 c.c.	4	9	10	6	1	0
Total			8	16	14	7	2	3

All patients received general anesthesia consisting of intravenous Pentothal sodium supplemented with either inhalation gas, oxygen, ether, or nitrous oxide and oxygen. Only 8 patients required an endotracheal tube. This type of anesthesia was used because of rapidity of induction and familiarity with its use by our anesthesia department. Conduction anesthesia was felt to be contraindicated in most cases because of the presence of internal bleeding.

TABLE X. SURGICAL PROCEDURES

PROCEDURE	1956	1957	TOTAL
Salpingectomy alone	12	23	35
Salpingo-oophorectomy	3	3	6
Salpingectomy-appendectomy	4	0	4
Total abdominal hysterectomy and bilateral salpingectomy	0	1	1
Total abdominal hysterectomy and bilateral salpingectomy (unsuspected ectopic pregnancy)	1	0	1
Salpingectomy-myomectomy	0	1	1
Resection of ovary	0	2	2
Total	20	30	50

The surgical procedures used in this series are listed in Table X. The most important step in all cases was to clamp the source of bleeding at the earliest possible opportunity. Second, conservative surgery was attempted at all times. Once the bleeding had been controlled and the surgical specimen removed, a thorough inspection of the pelvis was carried out. An attempt was made to visualize the uterus as well as both ovaries and the remaining Fallopian tube. In several cases, the opposite tube was found to contain a hydrosalpinx or showed evidence of chronic salpingitis. In the face of gross bleeding, it was felt unwise to disturb or remove the other diseased tube. During the early period of this study, several incidental appendectomies were also performed at the time of the salpingectomy. This was later abandoned, however, as an unwise procedure in the face of free blood as a culture medium in the abdominal cavity. There were 2 patients who had had previous ectopic pregnancies. In one patient, a total abdominal hysterectomy was carried out at the time of the second salpingectomy while in the other patient salpingectomy alone was performed. In both patients the amount of blood in the peritoneal cavity was found to be less than 500 c.c. and both were clinically in good condition at the time of operation. Removal of a nonfunctioning uterus was felt justifiable by the operator in the former case in the absence of extensive bleeding

or other complications at the time of operation. Thirty-nine patients underwent unilateral salpingectomy alone. In 6 patients, it was necessary to remove the ovary with the tube on the side involved because of implantation of the pregnancy on the ovary or because of severe compromise of the ovarian blood supply.

An attempt at conservative surgery with preservation of as much fertility as possible should be carried out. In all cases a complete salpingectomy should be done with cornual resection of the involved tube. We feel it is unwise to leave a partial tube as a potential site for a second ectopic pregnancy on the same side. In addition, these segments of tube usually do not remain patent and have very little peristaltic action. There are many authors today who do not feel that the entire tube need be sacrificed. They advocate removal of the conceptus with salvage of the oviduct without closing the tube. They feel that, by conservative surgery, tubal pregnancy can be followed by uterine pregnancy in a number of cases.[4, 19] There was one case in this series in which a bilateral tubal resection had been carried out for severe pelvic inflammatory disease. The patient was admitted approximately one year later with a tubal pregnancy which had so completely distorted the involved side of the pelvis that we were unable to localize the site of the pregnancy. On the opposite side, there was a segment of tube absent indicating that a resection had been carried out. It is our opinion, therefore, that a complete salpingectomy should be carried out with preservation of the opposite side if at all possible, as well as preservation of as much ovarian function as possible.

Pathology

In regard to the microscopic pathology, one must find some evidence of pregnancy tissue, villi or decidua, in order to make the diagnosis of ectopic gestation. In the case of tubal pregnancy, one would expect equal involvement of the right and left sides. In this series, there were 21 ectopic pregnancies on the right and 27 on the left (Table XI). There were 2 ovarian pregnancies, one occurring on each side. The site of the pregnancy within the tube likewise varied. Implantation occurred most frequently in the distal portion of the tube and decreased in frequency as one approaches the uterus.

TABLE XI. SURGICAL DATA

	TUBE INVOLVED (48 CASES)		LOCATION OF PREGNANCY WITHIN TUBE			OVARY (2 CASES)	
YEAR	RIGHT	LEFT	PROXIMAL 1/3	MID 1/3	DISTAL 1/3	RIGHT	LEFT
1956	10	10	5	8	7	0	0
1957	11	17	3	8	17	1	1
Total	21 (43.7%)	27 (56.3%)	8 (16.7%)	16 (33.3%)	24 (50%)	1 (50%)	1 (50%)

Twenty-four cases occurred in the distal one third, 16 cases in the middle-third, and 8 cases in the proximal one third of the tube. There was one interstitial pregnancy which had ruptured and secondarily became implanted along the broad ligament adjacent to the fundus of the uterus. There were 2 ovarian pregnancies which were considered primary. In both cases, there were trophoblastic villi within the substance of the ovary and in both cases the tubes bilaterally appeared perfectly normal. At the time of operation, there were 37 patients with ruptured tubal pregnancies and 11 unruptured

which were confirmed pathologically. One would expect the incidence of ruptured ectopic pregnancy to be high for the diagnosis in most cases is not made until the time of rupture. This also depends to some degree on the age of the gestation. Word[21] felt that ruptured tubal pregnancy occurs about 20,000 times annually in the United States.

Morbidity and Mortality

The morbidity is not recorded strictly according to the standard of the American Committee on Maternal Welfare. The patients were divided into two groups: (1) those who at no time during their hospital stay had a temperature elevation above 99° F., and (2) those who had a temperature over 100° F. on one or more days during their hospital stay. Thirty-five patients (70 per cent) fell in the second group. In most cases the elevation of temperature did not persist for more than approximately 24 to 36 hours and was felt to be due in a large number of cases to a foreign body reaction, absorption of blood from the peritoneal cavity. In this group there were 2 cases of postoperative pneumonia, 2 urinary tract infections, one case of diarrhea, etiology undetermined, one wound infection, and one mild transfusion reaction. The average hospital stay for the entire series was 8 days. There were 23 patients treated with antibiotics postoperatively. All of the above-mentioned postoperative complications were treated with antibiotics. We do not feel that antibiotics should be used prophylactically in all ectopic pregnancies but certainly feel that they will reduce the severity of complications when indicated. The antibiotics used in most cases were penicillin and streptomycin unless a specific organism was isolated which was sensitive to a specific antibiotic. Of the 4 patients in whom an incidental appendectomy was done at the time of laparotomy, 2 ran a temperature above 100° F. during the postoperative course. None of the 4 were given antibiotics. Two patients had some difficulty postoperatively with abdominal distention, one of whom required Wangensteen suction for approximately 24 hours. Patients who have a large amount of blood in the abdomen usually develop postoperative ileus no matter how gently the operation is performed or how little the pelvic organs are disturbed.[6] We found this complication to occur rather infrequently in this series.

There was no maternal death. Prior to 1940, the per cent of maternal deaths from ectopic pregnancy has been reported from 3 per cent to as high as 12 per cent.[1, 6, 14] More recently, however, the mortality rate has dropped to from 1 to 3 per cent.[6, 7, 13, 17]

Summary and Conclusions

1. Ectopic pregnancy is defined.

2. The relation of age, race, and gravidity with reference to the incidence of ectopic pregnancy is considered.

3. Theories regarding the etiology of ectopic pregnancy are reviewed. The symptom complex and physical findings are likewise discussed.

4. Diagnostic procedures with the increased importance of culdocentesis and colpotomy are stressed.

5. There were 70 cases of suspected ectopic pregnancy in which laparotomy was performed. Fifty cases were performed at the time of operation for a correct preoperative diagnosis of 70 per cent.

6. Successful management of the condition depends on: (a) being "ectopic minded," (b) increased use of diagnostic procedures, (c) early operation, and (d) adequate blood replacement early and the use of antibiotics when indicated.

7. Maternal morbidity and postoperative complications in this series were infrequent. There was no maternal death.

References

1. Anderson, G. W.: Am. J. Obst. & Gynec. **61**: 312, 1951.
2. Asherman, J. G.: Obst. & Gynec. **6**: 619, 1955.
3. Beacham, W. D., Webster, H. D., and Beacham, D. W.: Am. J. Obst. & Gynec. **72**: 830, 1956.
4. Bender, S.: J. Obst. & Gynaec. Brit. Emp. **63**: 400, 1956.
5. Caldwell, J.: Am. J. Obst. & Gynec. **72**: 1227, 1956.
6. Collins, C. G., Beacham, W. D., and Beacham, D. W.: Am. J. Obst. & Gynec. **57**: 1144, 1949.
7. Donovan, W. H.: Obst. & Gynec. **7**: 694, 1956.
8. Draa, C. C., and Baum, H. C.: Am. J. Obst. & Gynec. **61**: 300, 1951.
9. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc.
10. Erhardt, C. L.: Am. J. Pub. Health **46**: 828, 1956.
11. Fontanilla, J., and Anderson, G. W.: Am. J. Obst. & Gynec. **70**: 312, 1955.
12. Halbrecht, I.: Obst. & Gynec. **10**: 73, 1957.
13. Kohl, S. G.: New York J. Med. **56**: 850, 1956.
14. Leff, B., and Winson, S. G.: Am. J. Obst. & Gynec. **53**: 296, 1947.
15. Lucci, J. A.: Am. J. Obst. & Gynec. **66**: 1178, 1953.
16. Novak, E., and Novak, E. R.: Textbook of Gynecology, ed. 5, Baltimore, 1955, Williams & Wilkins Company, p. 535.
17. Parker, S. L., Jr., and Parker, R. J.: Am. J. Obst. & Gynec. **74**: 1174, 1957.
18. Spiegelberg, O.: Arch. Gynäk. **13**: 73, 1878.
19. Tompkins, P.: Fertil. & Steril. **7**: 448, 1956.
20. Ware, H. H., Jr., and Winston, W. O.: Obst. & Gynec. **4**: 29, 1954.
21. Word, B.: Obst. & Gynec. **8**: 627, 1956.
22. Word, E.: Surg. Gynec. & Obst. **92**: 333, 1951.

ECTOPIC PREGNANCY*

A Review of 481 Cases

J. T. Armstrong, M.D., Seward H. Wills, M.D., Jack Moore, M.D., and A. E. Lauden, M.D., Houston, Texas

(From the Department of Obstetrics and Gynecology, Baylor University College of Medicine, Texas Medical Center)

THIS is a review of 481 cases of ectopic pregnancy. An attempt will be made to evaluate the symptoms, physical findings, and diagnostic procedures that proved of value in making the diagnosis. Interest in ectopic pregnancy has been maintained through the years because of the diagnostic problems inherent in the disease. This review adds 93 cases that occurred in 1956 to the 388 cases previously reported.[1] We plan to continue the series for several more years to determine whether there is a statistical increase in the incidence rate.

Material for Study

The material for study was extracted from case histories during the years 1951 to 1956, inclusive, in two Houston, Texas, hospitals. Jefferson Davis Hospital (Hospital A) accommodates indigent patients and Hermann Hospital (Hospital B) accommodates both indigent and private patients.

Incidence

Table I illustrates the cases by years and the number of deaths. From 1953 to 1956 a rather uniform rate was maintained. Hospital A had 192 cases while Hospital B had 289. The 4 deaths represent 0.83 per cent of the series.

Table I. Incidence by Years

Year	Hospital		Total	Deaths
	A	B		
1951	19	36	55	
1952	35	37	72	
1953	43	44	87	2
1954	32	56	88	
1955	31	55	86	1
1956	32	61	93	1
Total	192	289	481	4
Mortality				0.83%

Table II lists the number of ectopic pregnancies and deaths according to types. The 3 deaths in 469 tubal pregnancies were all considered preventable by the Maternal Mortality Committee. One death, in a case of abdominal pregnancy,

*Presented at the Twenty-ninth Annual Meeting of The Texas Association of Obstetricians and Gynecologists, Galveston, Texas, Feb. 15, 1958.

caused by cardiac arrest while the abdomen was being incised, has not been reviewed. One of the 2 ovarian pregnancies was suspected and the other was considered to be a tuboovarian abscess. The patient with the cervical pregnancy bled so profusely that hysterectomy was necessary. Three living babies were salvaged from the 9 abdominal pregnancies.

TABLE II. TYPES OF ECTOPIC PREGNANCIES IN COMBINED SERIES OF 481 CASES

		DEATHS	LIVE BABY
Tubal	469	3	
Abdominal	9	1	3
Ovarian	2		
Cervical	1		
Repeat ectopic	11 (2.2%)		
Simultaneous intra- and extrauterine	2 (0.41%)		

There were 11 causes of repeated tubal ectopic pregnancies. One of these patients had a third tubal pregnancy.

The 2 simultaneous intra- and extrauterine pregnancies were very interesting. One progressed to 23 weeks and was diagnosed as a twin intrauterine pregnancy complicated by a large ovarian cystoma. The tubal pregnancy had not ruptured. The patient was delivered of the intrauterine 1 pound, 7 ounce fetus at 29 weeks and it died after 2 days. The second patient had a repair of the damage done by the rupture of an interstitial tubal pregnancy; however, the intrauterine pregnancy was aborted 2 days later.

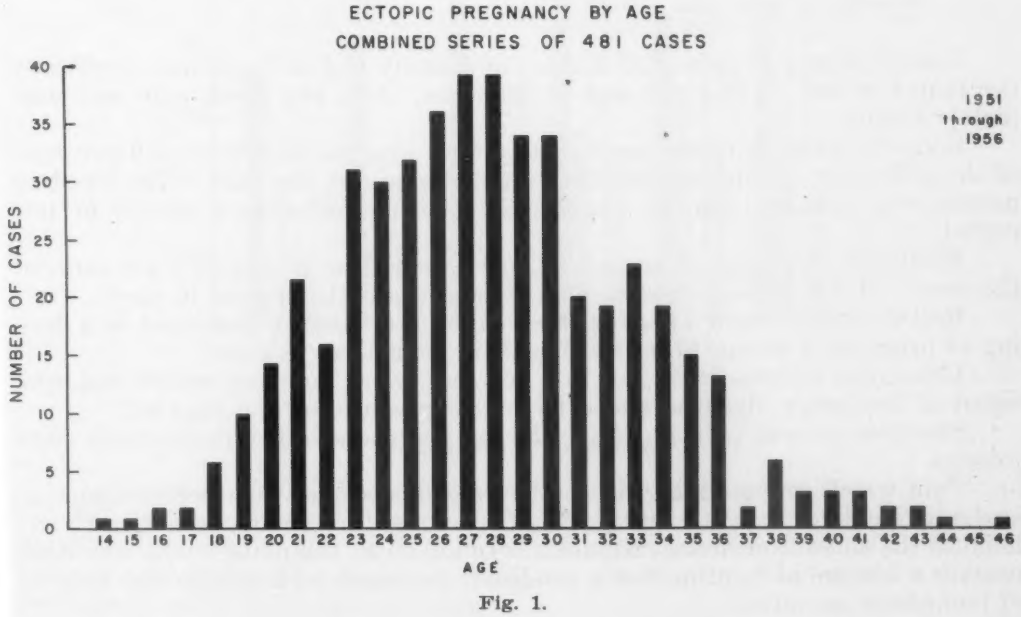


Fig. 1.

Several cases deserve special mention. One tubal ectopic pregnancy followed a Pomeroy tubal sterilization operation. One patient had a partial salpingectomy of her only remaining tube and has been delivered normally since her operation. In one patient an interstitial pregnancy ruptured into the cecum and presented only intestinal bleeding of almost exsanguinating proportions.

The number of ectopic pregnancies and live births by years are shown in Table III. In the combined series, it will be seen that the rate per 1,000 live

births increased from 6.6 in 1951 to 10.2 in 1956. The distribution of cases by age is shown in Fig. 1. The usual reproductive life span is covered. The greatest number of patients were 27 and 28 years old.

TABLE III. NUMBER OF ECTOPIC PREGNANCIES PER 1,000 LIVE BIRTHS

	NO. OF ECTOPIC PREGNANCIES	NO. OF BIRTHS	NUMBER / 1,000 LIVE BIRTHS
1951	55	8,292	6.6
1952	72	8,149	8.8
1953	87	9,071	9.5
1954	88	9,208	9.5
1955	86	9,072	9.4
1956	93	9,036	10.2

Symptoms

The most common complaints are listed in the order of frequency in Table IV. Statistics were taken from the records on which some specific reference was made. In many acute emergency cases the records were sketchy and very little positive information was mentioned.

TABLE IV. SYMPTOMS IN ORDER OF FREQUENCY IN COMBINED SERIES OF 481 CASES

SYMPTOMS	NO.	%
Abdominal pain	464	96.4
Amenorrhea and/or irregular bleeding	423	87.9
Feeling of faintness or weakness	182	37.8
Rectal pain and/or tenesmus	77	16.0
Urinary symptoms	75	15.8
Shoulder or neck pain	62	12.8

Lower abdominal pain of all degrees of severity and all types was specifically mentioned in 464, or 96.4 per cent, of the cases. In a few cases, pain was completely absent.

Some irregularity of the menstrual pattern occurred in 423, or 87.9 per cent, of the 481 cases. Abnormal bleeding usually preceded the pain. The bleeding pattern was usually irregular bleeding or spotting following a missed or late period.

Weakness, faintness, or actual syncope occurred in 182, or 37.8 per cent, of the cases. Many of these cases were acute and the patients were in shock.

Rectal complaints in 77, or 16.0 per cent, were usually described as a feeling of pressure, a strong urge to defecate, or painful defecation.

Urinary symptoms in 75, or 15.8 per cent, were not very severe and consisted of frequency, dysuria, and a feeling of pressure on the bladder.

Shoulder or neck pain in 62, or 12.8 per cent, was rather pronounced when present.

Pain which was originally in the lower abdomen and then became generalized and was later manifest in the shoulder or neck apparently was directly related to the amount of hemoperitoneum. In addition, the patient who was weak or gave a history of fainting was a candidate for shock and usually was in need of immediate operation.

Physical Findings

The important positive findings are shown in Table V. Pressure over the lower abdomen produced pain in 446, or 92.7 per cent. Pelvic tenderness was present in 406, or 84.4 per cent. A palpable mass was described in 324, or 67.3 per cent. This varied from a well-defined, discrete, measurable mass to diffuse thickness or bulging in the cul-de-sac of Douglas. Hemoperitoneum of some degree was proved by culdocentesis in 272 cases or 58.4 per cent, plus one proved

by abdominal paracentesis. Rebound tenderness in 193, or 40.1 per cent, and abdominal wall guarding or rigidity in 176, or 36.5 per cent, were recorded. It is believed that more emphasis should be given to examining the abdomen.

TABLE V. PHYSICAL FINDINGS IN COMBINED SERIES OF 481 CASES

		NO.	%
Abdominal tenderness		446	92.7
Pelvic tenderness		406	84.4
Palpable mass		324	67.3
Adnexal	236		
Cul-de-sac	88		
Culdocentesis positive for unclotted blood		272	58.4
Abdominal rebound tenderness		193	40.1
Abdominal wall guarding or rigidity		176	36.5
Shock on arrival or developed in hospital		80	16.6

Clinical shock was present in 80, or 16.6 per cent, in the 6 years studied. Only 9, or 9.6 per cent, of the 93 patients in 1956 were in shock. In 1956, the time from diagnosis to the time of operation was greatly reduced. It is believed that quicker treatment reduced the incidence of shock.

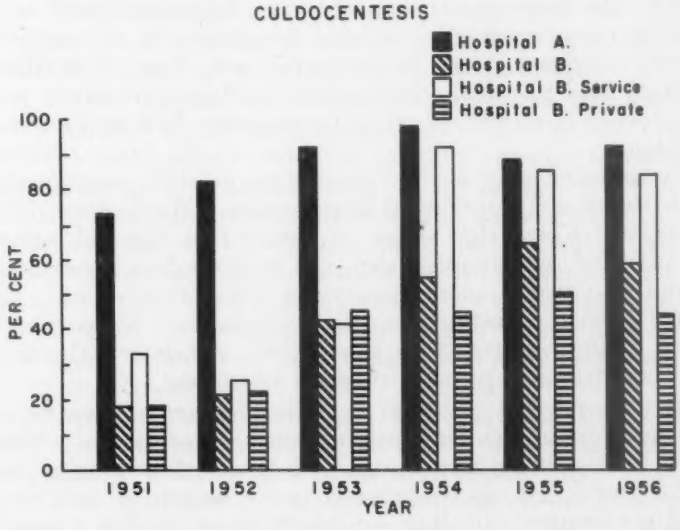


Fig. 2.

Diagnostic Procedures

As shown in Table VI, culdocentesis was utilized in 169, or 88.0 per cent, of the 192 cases in Hospital A and in 137, or 47.4 per cent, of the 289 cases in Hospital B, a total of 306, or 63.5 per cent, in the combined series. The number and per cent positive for unclotted blood are also shown. Culdocentesis did not produce blood in 34, or 11.1 per cent.

Posterior colpotomy was used in 6 cases in Hospitail A and in 32 cases in Hospital B. The ectopic pregnancy was removed vaginally in 15 cases, in 3 of which vaginal hysterectomy was also done. The colpotomy was strictly an aid to diagnosis in 23 cases prior to laparotomy. The rectum was entered one time when colpotomy was attempted.

The one abdominal paracentesis was an aid to diagnosis by accident. The patient was being investigated by the medical service for anemia and ascites when the hemoperitoneum was discovered.

Culdoscopy is mentioned only to record that it was not performed once.

Fig. 2 shows a very frequent and consistent use of culdocentesis in Hospital A. The use of culdocentesis has shown a gradual increase in Hospital B. The increase has been more on the indigent service than on the private service.

TABLE VI. PROCEDURES USED IN DIAGNOSIS OF 481 CASES

	HOSPITAL A		HOSPITAL B		COMBINED	
	NO.	%	NO.	%	NO.	%
Total	192	39.9	289	60.1	481	100.00
Culdocentesis	169	88.0	137	47.4	306	63.5
Positive for unclotted blood	148	87.5	124	90.5	272	88.9
Negative for unclotted blood	21	12.5	13	9.5	34	11.1
Colpotomy	6	3.1	32	11.0	38	7.9
With treatment vaginally	2	1.0	13	4.4	15	3.1
Prior to laparotomy	4	2.0	19	6.5	23	4.7
Abdominal paracentesis	1				1	
Culdoscopy					0	

Comment

An acute sense of suspicion or being "ectopic conscious" helps a great deal in making an accurate diagnosis in cases of ectopic pregnancy. Many conditions, as judged by the large variety of tentative diagnoses listed in the cases in this series, must be considered when ectopic pregnancy is a possibility. We attempt to make our residents "ectopic pregnancy conscions." If they encounter many of the history and physical examination findings previously presented, we expect them to proceed to eliminate ectopic pregnancy first and not rule it out as a last consideration.

Occasionally someone may wonder how many ectopic pregnancies would be self-correcting without early operative interference. Many do progress into the old or chronic state. From this series, it seems that the old ectopics become very extensive, infected, or involved with the surrounding structures and more extensive extirpative surgery is necessary for their correction. No statistics, however, are presented to substantiate this impression. We prefer to diagnose such pregnancies in their acute stage if possible. Their lethal possibilities are offset by early diagnosis and prompt surgical treatment.

An accurate history and physical examination are presented as the most important consideration in the diagnosis of ectopic pregnancy. The menstrual history seems to be the most important. So often it is similar to that with pregnancy in the uterus, i.e., amenorrhea of some length or an atypical period. Prolonged scant continuous bleeding or intermittent spotting usually follows. The onset of pain usually occurs later. Pain was most often described as a soreness with a tendency to be more severe intermittently. The other most common symptoms, weakness or syncope, rectal pain or pressure, and shoulder pain are usually produced by intra-abdominal bleeding. The more pronounced the bleeding may be, the more pronounced are the symptoms and usually the patient's situation is more precarious.

The physical examination usually reveals findings that can be correlated directly with these historical findings. Abdominal tenderness in 92.7 per cent, rebound tenderness in 40.1 per cent, and muscle guarding or rigidity in 36.5 per cent emphasize the value of the abdominal examination. Very frequently pelvic pain is so great that the patient cannot tolerate bimanual examination. The pelvic examination should be very gentle to elicit tenderness and masses.

Shock on arrival or its development in the hospital was present in 16.6 per cent of the cases in the entire series; however, the rate was 9.6 per cent in 93 cases in 1956. We believe that better diagnosis was obtained and treatment was instituted earlier.

Culdocentesis cannot be overemphasized as an aid to diagnosis and its increasing usage will result in earlier treatment. In 1956, in Hospital A, 29 of the 32 cases were examined by culdocentesis. As to the interval between admission and time of operation, 21 patients were operated upon in the first hour, 6 by the second hour, 2 by the third hour, and 1 by the fourth hour. The 2 cases beyond this time were old and one of them was an ovarian ectopic pregnancy.

Anatomical derangements, such as adhesions, may make it impossible to get a needle in the peritoneal cavity. No blood was aspirated in 34, or 11.1 per cent, of the 306 cases examined by culdocentesis. It was necessary to repeat the examination at intervals in some cases before blood was aspirated. It is to be emphasized that a negative result does not eliminate an ectopic pregnancy. One death in this series was directly the result of such an error. The patient died without operation with approximately 3,000 c.c. of blood in the peritoneal cavity. Hemoperitoneum may result from other causes and a few cases may be misdiagnosed. Two cases not in this series in 1957 were ruptured aneurysms. One patient was saved by prompt intervention.

Early in this series, most of the culdocenteses were done in the operating room; however, now most of them are done in offices or emergency rooms. It is valuable to the residents at odd hours of the night and costly errors are reduced to a minimum. The records show that 3 patients from whom blood was aspirated were hospitalized, dismissed, and readmitted for operation. The rectum was entered in one of the 3 when colpotomy was attempted. She was dismissed, readmitted, and operated upon one week later.

Aspiration of the cul-de-sac seems more practical than abdominal paracentesis for investigation of any abdominal fluid. The medical and many of the surgical specialties could afford to add it to their avenues of examination.

Posterior colpotomy was used in only 35 instances, or 7.9 per cent, of the 481 cases; 15 of the 38 cases, however, resulted in vaginal removal of the ectopic pregnancy, a percentage of 3.1. Seven patients so treated in 1956 spent a total of 31 postoperative days in the hospital or an average of 4.4 days, in spite of one who spent 10 days. The long stay was in the case of vaginal hysterectomy. The remaining 6 spent an average of 3.3 days. Thirteen of the 15 were in Hospital B. Vaginal removal of an ectopic pregnancy seems simple when the involved tube is readily available.

Chronic inflammatory disease of the Fallopian tubes has long been considered an etiological factor in ectopic pregnancy; however, the same process frequently completely occludes the tubes and makes any form of pregnancy impossible. On the supposition that the advent of chemotherapeutic and antibiotic drugs might salvage more Fallopian tubes and leave them partially occluded, it was deduced that ectopic pregnancies should increase when compared to a given number of uterine pregnancies. Statistics for the whole community are not available; however, in the two facilities studied for 6 years, there seems to be an increase.

Conclusions

1. Four hundred and eighty one cases of ectopic pregnancy were reviewed. The cases were treated in two Houston, Texas, hospitals from 1951 to 1956, inclusive.

2. There was an increase in the number of ectopic pregnancies per 1,000 live births.

3. An attempt is made to review the symptoms, physical findings, and aids to diagnosis which were responsible for the patients' receiving definitive surgical treatment.

4. The use of culdocentesis proved to be an invaluable aid to diagnosis. The more frequent use of culdocentesis has reduced the time of observation before treatment.

5. The mortality rate in the series was 0.83 per cent.

Reference

1. Armstrong, J. T., Wills, S. H., and Moore, Jack: South. M. J. 50: 587, 1957.

426 Hermann Professional Bldg.
6410 Fannin Street
Houston 25, Texas

Discussion

DR. ASA WATSON, Fort Worth, Texas.—Dr. Armstrong and his associates have presented a review of a subject that should be of great interest to all physicians who treat women. All of us know that feeling of uncertainty that accompanies the admission of a patient to the hospital with lower abdominal pain and unusual uterine bleeding. We say, "I think it is probably an ectopic, but it might be threatened abortion, salpingitis, etc." Frog, rabbit, and other laboratory tests may or may not be helpful, and even when they are, they are time consuming. Probably the most helpful aid to diagnosis is the increasing use of the posterior cul-de-sac puncture, which is easily and quickly performed and relatively painless. The colpotomy is useful when culdocentesis is negative and the history is typical. The case of ruptured ectopic pregnancy with shock, abdominal distention, abdominal pain, bulging cul-de-sac, and pelvic mass is typical and should be easily diagnosed and quickly treated. With better anesthesia, blood available in adequate quantities, and use of pressor drugs, it now seems best to treat shock and operate at the same time in an effort to stop bleeding, rather than to treat shock and wait for the patient to respond and then operate. The rapid improvement in the patient's condition from nothing more than placing a clamp on the mesosalpinx is familiar to us all.

The more rapid diagnosis and surgical intervention will practically eliminate death as a result of ectopic pregnancy.

At Harris Hospital in Fort Worth, in the 5 year period from 1953 to 1957, there occurred 135 ectopic pregnancies with no deaths (Table I).

Table I. Ectopic Pregnancies at Harris Hospital

Year	Incomplete Abortions	Ectopic Pregnancies	Deliveries
1953	255	24	3610
1954	253	24	3795
1955	266	24	3835
1956	330	35	4462
1957	310	28	5348
Total	1,414	135*	21,050

*No deaths due to ectopic pregnancy.

There was a total of 22,464 pregnancies, including, 1,414 incomplete abortions.

The two main presenting symptoms were abdominal pain and uterine bleeding. It would be interesting to know how many of these were diagnosed unruptured.

The years 1953, 1954, and 1955 show almost identical figures with a definite increase in ectopic pregnancies in 1956 when the first increase in total pregnancies was notable. In the following year (1957), however with an increase of 1,500 pregnancies over 1955, there occurred only 28 ectopic pregnancies. This does not represent an appreciable increase. The figures from this one hospital and the years selected for review show a tendency toward an increased number of ectopics, but also an increased number of pregnancies. Before any definite conclusions can be drawn, further reviews will be necessary.

INTRAFOLLICULAR IMPLANTATION

A Case Report of an Early Primary Ovarian Pregnancy

P. A. S. Sahay, M.B., B.S., B.Sc., Halifax, Yorkshire, England

(From the Department of Obstetrics and Gynecology, General Hospital and Royal Halifax Infirmary)

CASES of primary ovarian pregnancy have been reported with increasing frequency recently. Establishing the authenticity in many cases, however, may be very difficult because of gross distortion of the anatomy and extensive tissue reaction following the rupture of the advancing ovarian pregnancy. A case of ovarian pregnancy is reported here in which a chance rupture after amenorrhea of only 37 days was instrumental in bringing out certain interesting features.

Mrs. E. P., aged 28 years, para 0, while teaching at school on March 7, 1958, was suddenly taken ill with acute lower abdominal pain on the right side and was carried home when she fainted. About 2 hours later she developed diarrhea and vomiting, the pain became more or less generalized over the lower abdomen and was accompanied by shoulder pain, mainly on the right side. She was sent to the surgical ward at the Royal Halifax Infirmary 6 hours later, with a diagnosis of probable acute appendicitis.

Her past history was noncontributory. Her menstruation occurred in a regular cycle of 25 days and her last menstrual period was on March 1, 1958, which she thought had ended on March 5, 1958. On further interrogation however, she agreed that her last period was delayed by 5 days. Before that she had menstruated on Jan. 30, 1958. For 2 days before admission, though the bleeding had eased, it had not actually stopped. Her pain was relieved by defecation. She had 5 loose bowel movements and vomited 6 times from the time of the onset of the pain.

On admission she did not look seriously ill, but appeared to be anemic and was very nervous. Her temperature was 96.4° F., pulse 84 per minute, and blood pressure 80/50. There was no abdominal tenderness, guarding, or rigidity but some rebound tenderness was suspected. Bowel sounds were present. Both pelvic and rectal examinations were inconclusive, and no definite mass was felt in the pelvis nor was it possible to elicit any tenderness. The hemoglobin was 80 per cent, white-cell count 25,000, polymorphonuclear leukocytes 92 per cent, and lymphocytes 8 per cent. An intravenous drip of 5 per cent glucose was started which brought the blood pressure up to 106/70 and she was put under observation.

Gynecological consultation was sought 4 hours later. The condition of the patient had altered by then. She looked exsanguinated, anxious, and restless. Her pulse rate had risen to 120 per minute. The blood pressure was maintained at 100/70. There was marked distention of the abdomen, which was hyperresonant all over, including the flanks. Percussion and even light palpation produced acute shoulder pain and the lower abdomen was generally tender. No masses could be palpated in the abdomen and bowel sounds were present. Pelvic examination produced extreme pain but, besides a doughiness in the fornices, no definite mass was felt. A dark chocolate-brown discharge was noted on the examining

finger. Rectal examination also failed to show the presence of any mass or localized tenderness. A provisional diagnosis of ruptured ectopic pregnancy was made. A blood transfusion was started and she was taken to the operating room.

On examination under anesthesia, the uterus was very easily palpable, small, almost hypoplastic, firm, anteverted, and freely mobile; the cervix was firm and closed. No masses were palpable in the fornices. No curettings were obtained. A laparotomy through a midline subumbilical incision was performed. The peritoneal cavity contained 1,000 ml. of free

Fig. 1.—Sketch showing the gestation sac, rupture, and the line of excision.

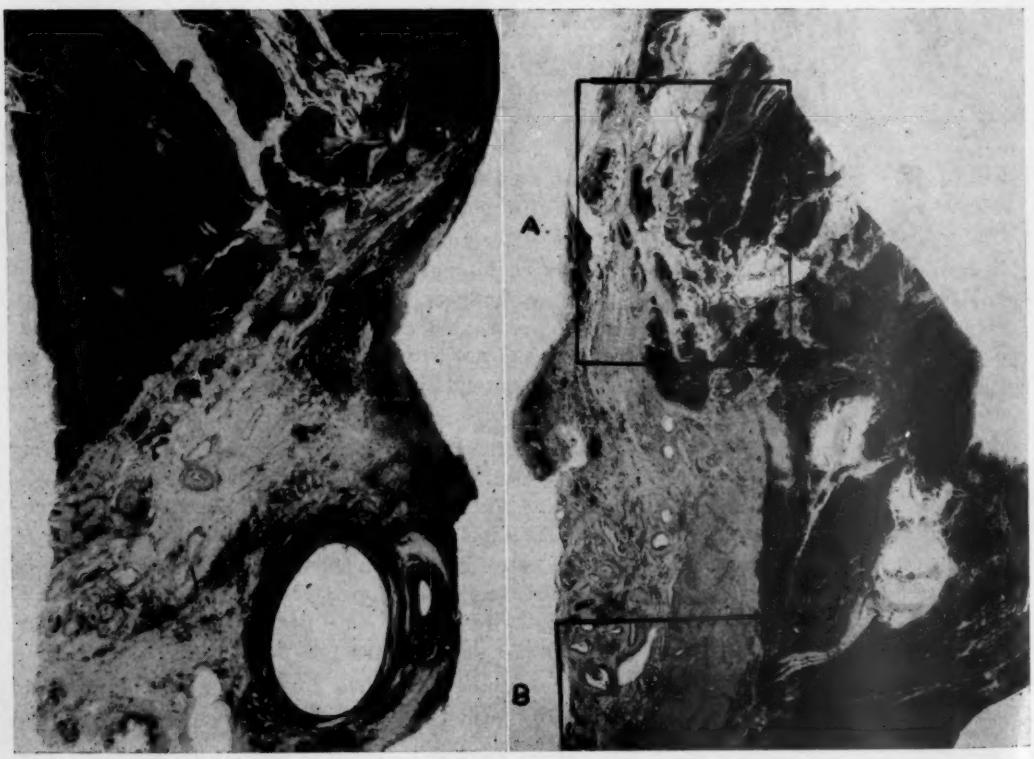


Fig. 2. Fig. 3.

Fig. 2.—Section showing extensive hemorrhage in the gestation sac and ovarian tissue in its wall. (×8.5; reduced ⅙.)

Fig. 3.—Section showing the relative positions of areas marked *A* and *B*, selected for higher magnification later. Note, in the wall, convolutions of the corpus luteum lining the sac. (×8.5; reduced ⅙.)

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Section showing the area marked *A* in Fig. 3, under higher-power magnification. Note the ovarian stroma on the left in the wall and chorionic villi at 12 and 4 o'clock positions. (×15.5; reduced ⅙.)

Fig. 5.—Section showing the group of chorionic villi shown in 4 o'clock position in Fig. 4. (×108; reduced ⅙.)

Fig. 6.—Section showing area marked *B* in Fig. 3. Note, in the wall of the sac, marked compression of the convolutions of the corpus luteum evidently due to the pressure from the hemorrhage in the sac. (×15.5; reduced ⅙.)

blood and approximately 400 ml. of blood clots. Both tubes, the left ovary, the uterus, and the broad ligaments were perfectly normal. The right ovary contained what appeared to be a hemorrhagic follicular cyst, 2 cm. in diameter, which on closer inspection showed a very small rupture through which fresh blood was freely escaping into the peritoneal cavity (Fig. 1). The rest of the right ovary appeared normal. The "cyst" was removed by wedge resection, and almost three-fourths of the right ovary was left. Hemostasis was achieved by interrupted through-and-through catgut sutures along the line of excision. The patient received a total of 2,000 ml. of blood. She made an uneventful recovery and was discharged on March 23, 1958, 15 days after operation.

Pathological Findings.—On section, the gross appearance of the mass was that of a cystic cavity filled with organized blood clots and some fresh blood. On closer inspection, in the center of the cut surface, there was a cavity 0.8 cm. in diameter, lined by a thin, gray, shining membrane. It did not contain a fetus. The wall apparently contained ovarian tissue, including a small atretic follicle in the cystic stage, confirmed by microscopic examination (Fig. 2). Another section (marked *A* in Fig. 3 and seen under higher power in Fig. 4) showed a hemorrhagic area containing groups of chorionic villi and ovarian stroma in the wall of the cavity. The chorionic villi made a striking picture under high-power magnification (Fig. 5). Lower down, the structures in the wall presented a characteristic ovarian appearance and convolutions of the corpus luteum could be easily made out, evidently under compression by hemorrhage in its own cavity. Examination of the area marked *B* (Fig. 3, shown under higher magnification in Fig. 6) confirms this.

Comment

This is a case of a primary ovarian pregnancy in which the implantation of the ovum has taken place in its own follicle. Fortunately, the abdomen was opened when the pregnancy was early enough to be confined entirely inside a very limited area of the ovary concerned, leaving the rest of the ovarian tissue unaffected. But for the excessive intra-abdominal hemorrhage, macroscopically it could have been mistaken for a ruptured hemorrhagic follicular cyst of the ovary. Besides easily fulfilling the widely quoted Spiegelberg's criteria of diagnosis, this case would also have been acceptable to both Leopold and Sutton, who, as quoted by Gibson,[2] did not accept any case as authentic unless the implantation was intrafollicular. In 2 recently reported cases,[1, 2] the implantation was extrafollicular. Novak and Novak[3] agreed that implantation can be either intra- or extrafollicular. In most cases, however, the exact method of implantation may not be easily established.

I wish to thank Mr. J. N. I. Emblin for permission to publish this case and for his advice in the preparation of the paper. I am indebted to Dr. G. T. Ashley and Mr. P. Howarth, both of the Anatomy department, Manchester University, for the painstaking photography.

References

1. Durburg, J. R., and Grimes, H. G.: Am. J. Obst. & Gynec. 75: 285, 1958.
2. Gibson, G. B.: J. Obst. & Gynaec. Brit. Emp. 64: 905, 1957.
3. Novak, E., and Novak, E. R.: Gynecologic and Obstetric Pathology, ed. 4, Philadelphia, 1958, W. B. Saunders Company, p. 483.

HYPOFIBRINOGENEMIA AND ABO HETEROSPECIFIC PREGNANCY

A Preliminary Report

CHRISTOPHER T. REILLY, M.D., AND ALEXANDER J. ZITO, M.D.,
PATERSON, N. J.

(From the Department of Obstetrics, Paterson General Hospital, and the Maple Medical Laboratory, Ridgewood)

HYPOFIBRINOGENEMIA in obstetrics is almost always associated with other obstetrical complications. Most frequently reported are abruptio placentae,[18] intrauterine death of the fetus with prolonged retention,[16] and amniotic fluid embolism.[5, 11, 15] In addition, Pritchard[13] has reported that hypofibrinogenemia can be further aggravated by the accidental administration of an incompatible blood transfusion into the maternal circulation. Not only does incompatible blood cause abnormalities in the hemostatic mechanism in humans, but also in experimental animals. Some of the changes include thrombocytopenia, prolongation of the clotting time and prothrombin time, hypofibrinogenemia, and increased fibrinolytic activity.

Most authors have accepted the theories advocated by Page, Fulton, and Glendening[10] on the subject of the production of hypofibrinogenemia. Thromboplastin, liberated from the placenta and decidua, is forced into the maternal circulation, converting fibrinogen into fibrin, which is deposited along the blood vessel walls in the maternal circulatory system and later removed by fibrinolysis. Stouffer[17] was impressed by the large amount of fibrin deposited in the placentas in cases of hypofibrinogenemia associated with intrauterine retention of a dead fetus. It must be stated, however, that many of the contributing factors and details of the exact mechanism of the production of hypofibrinogenemia require further study.

If one assumes that some substance enters the maternal circulation to cause hypofibrinogenemia, then some clarification is needed to explain just what an incompatible blood transfusion would add to the maternal circulation that a compatible blood transfusion would not add, other than heterospecific antigen. It is indeed very interesting that many of the cases of prolonged retention of a dead fetus which resulted in hypofibrinogenemia also, supposedly coincidentally, show isoimmunization,[2, 7, 16, 17] and that, in most of the other cases of hypofibrinogenemia, the associated complications of pregnancy could have resulted in placing fetal antigens into the maternal circulation. The mechanism of this transfer will be discussed for each type of complication. The question raised is, of course, whether, if the antigen in any

given case is heterospecific, one can assume that the result would be similar to giving incompatible blood by transfusion. Would this explain why the fibrinogen level is not lowered in all cases of abruptio placentae or intrauterine retention of a dead fetus?

First a review of the three major associated complications is in order. Amniotic fluid can contain blood antigens. It is known that a certain number, probably 80 per cent, of fetuses are secretors.[4] That is, they secrete in their saliva and amniotic fluid the same antigens that are normally found in their erythrocytes. Therefore, amniotic fluid embolism, in the presence of a secretor, would introduce these antigens into the maternal circulation.

Premature separation of the placenta does not rule out the possibility of fetal blood entering the maternal circulation. In fact, even in normal pregnancies a certain minimal amount of fetal blood is thought to enter the maternal circulation, during the prenatal period, and especially during the third stage of labor from the normal retroplacental clot. Studies done by Bromberg and associates[2, 3] have demonstrated in normal pregnancies that fetal hemoglobin was present in the maternal blood, and in the normal retroplacental clot of the same patients an even higher percentage of fetal hemoglobin was found. Any strong contraction occurring between the time of the delivery of the infant and of the placenta could force retroplacental blood into the maternal sinuses of the contracting uterus. This seems to confirm the theory of Potter[12] that more sensitization occurs at the time of delivery than during the entire pregnancy, in cases of Rh incompatibility. In addition, in sensitized individuals in the first few weeks following the delivery, marked rises in the Rh antibody titers are noted. Bromberg found unusually high levels of fetal hemoglobin in the maternal circulation in cases of premature separation of the placenta. Kennan[8] has noted a fall in fibrinogen during labor and delivery with a marked rise shortly after delivery. If heterospecificity is of any importance, then this fall would have been more pronounced had his series included only heterospecific type pregnancies.

Hartmann[6] in 1957 reported an unusual case of fibrinogen deficiency occurring in the second trimester of pregnancy. It was noted when the patient developed a cerebrovascular accident and subsequently recovered. The hypofibrinogenemia was acute, self-limiting, and the patient received no fibrinogen. It is of interest that at term, when this patient was delivered without complication, an old placental clot was noted and, in addition, the baby developed jaundice 12 hours after delivery. The jaundice deepened after 36 hours and eventually faded. The authors felt that there was suggestive but not conclusive evidence of a mild anti-A sensitization as the cause of this jaundice. This was considered to be coincidental and apparently was reported only for the sake of completeness.

A major portion of the reported cases of hypofibrinogenemia are associated with intrauterine retention of a dead fetus. The original cause of death in most of these cases is isoimmunization. In many others the cause is unknown and may well be ABO incompatibility or incompatibility to some other

antigen system. Reid[16] in 1953 reported 6 cases of maternal hypofibrinogenemia associated with long-standing intrauterine fetal death. Four of the patients had Rh sensitization. In one case the mother was type O Rh positive and the father was type B Rh positive, which is the setup for a possible B incompatibility. In the final case the mother was type B Rh positive and the husband was type O Rh positive, a combination which normally is not considered incompatible, but certainly does not rule out any of the more recently discovered blood antigens of importance. In any event, further absorption of a heterospecific antigen in the presence of a heterospecific pregnancy after fetal death occurs can be assumed, if the fetus was a secretor, since the amniotic fluid is absorbed.

Paxson[11] reported the high incidence of multiparity in cases of hypofibrinogenemia. This was reported without explanation other than the possibility that excessive uterine contractility in multiparous patients might be of importance. Could it be that sensitization must occur at the time of the first pregnancy before hypofibrinogenemia results in the future pregnancies?

Although it is frequently stated that the isoimmunization of the patient is considered to be of no significance in the production of hypofibrinogenemia, no extensive study has been reported either to prove or disprove that heterospecific pregnancy could cause or aggravate an already present hypofibrinogenemia. Frick and McKelvey[5] did consider incompatibility in a case of fetal death which they reported, even to the point of doing an indirect Coombs test with the father's erythrocytes and mother's serum. No incompatibility could be demonstrated. In this same case, however, no incompatibility could be demonstrated between the patient's blood and blood used for a transfusion. Nevertheless, a severe chill occurred after the administration of 250 c.c. of this fresh blood, suggesting some unknown incompatibility which was not detected by the usual laboratory tests. The original intent of the present study was to place on record the significance of heterospecific pregnancy and, since the early findings were extremely interesting, the present preliminary report was prepared in order to interest others in investigating this field.

Materials and Methods

The incidence of clinical hypofibrinogenemia in a 400 bed hospital is very low, and the number of cases very few indeed. Actually the few documented cases that were available to us all showed Rh incompatibility. Therefore, consideration was given to the possibility that subclinical levels of fibrinogen might be developing in patients without becoming low enough to cause hemorrhage. In addition, living babies would be involved in such a study and, since their blood type can be determined, the question of paternity need not be considered. Blood specimens were therefore taken from all mothers just prior to delivery and from the umbilical cord after delivery. Both clotted and oxalated samples were used. Since spinal was the type of anesthesia most frequently used in our hospital, we were able to have the anesthesiologist obtain the blood samples following the administration of the spinal anesthesia, at a time estimated to be approximately 5 minutes before the expected time of delivery of the baby. Maternal plasma fibrinogen was determined by the biuret method. ABO and Rh (D) blood typing was done on the cells from the oxalated specimens of both

the mother and baby by means of the slide method. If there was any doubt, the tube method was used for confirmation. A direct Coombs test was done on all babies born to Rh-negative mothers regardless of the baby's Rh factor. If the baby's blood was then, by these results, presumed to be compatible, the washed cells from the baby were cross-matched against the mother's serum by the indirect Coombs test method.

This is a pilot study of what we hope will be a continuous study of the many phases still requiring investigation. At this point, however, it was decided to change some of the methods, particularly the time of obtaining the specimens, and, therefore, these first 87 cases represent the total number of cases in the first phase of the survey. As yet, no attempt has been made to correlate clinical findings in these patients with the laboratory data. All of the cases in which specimens were obtained at the proper time were included in this report without any attempt to differentiate complicated cases.

Results

The patients were separated into two major groups: (1) those presumed to be homospecific as far as the ABO factors are concerned and with no Rh sensitization, and (2) those considered to be heterospecific or with definite Rh sensitization. The homospecific group was further divided into those in whom any ABO factor present in the baby was definitely present in the mother, and those in whom a certain percentage of babies could possibly have O and some of the mothers might possibly not have O factor. An example of such a case would be a mother with the genetic pattern of BB with a BO baby, yet they would both be type B blood. The incompatible group was divided into three groups: A incompatibility, B incompatibility, and Rh sensitization regardless of ABO factors. As can be noted in Table I, the results were over a wide range.

TABLE I

MOTHER'S TYPE	BABY'S TYPE	NO. OF CASES	RANGE (MG. %)	AVERAGE (MG. %)
Compatible Combinations.—				
O	O	19	165 to 385	292
AB	AB	1	312	312
A	O	12	150 to 295	235
B	O	4	195 to 385	291
Total: All ABO factors in baby, also in mother		36	150 to 385	273
A	A	17	150 to 350	259
B	B	5	195 to 295	253
AB	A	2	354 to 370	362
AB	B	2	336 to 425	381
Total: Possible O in baby and not in mother		26	150 to 425	275
Total of all probable compatible combinations		62	150 to 425	274
Incompatible Combinations.—				
O	A	9	165 to 295	208
B	AB	4	165 to 295	215
Total: All A incompatibility		13	165 to 295	210
O	B	6	210 to 315	248
A	AB	3	110 to 260	188
A	B	2	165 to 210	188
Total: All B incompatibility		11	110 to 315	221
A Rh (D) negative sensitized	A Rh (D) positive (positive Coombs)	1	165	165
Total of all incompatible combinations		25	110 to 315	213
Total of all cases		87	110 to 425	256

The average of all fibrinogen levels at approximately 5 minutes before delivery was 256 mg. per cent. The difference in the average fibrinogen level between compatible and incompatible pregnancies was 61 mg. per cent. There were 2 cases in the series in which the direct Coombs tests on the babies' blood were positive. One, as noted in Table I, was due to Rh (D) incompatibility and the fibrinogen level was 165 mg. per cent. The other was a B mother with an AB baby and the level was also 165 mg. per cent. Both babies developed jaundice. A third case of Rh sensitization was not included in this series because blood was obtained before labor and just after the placenta was delivered instead of at the usual time. The fibrinogen on both occasions was 110 mg. per cent.

Another interesting observation is that the highest result in the A incompatible group occurred in a case in which the baby's cells gave only a weak reaction to the anti-A serum. The cross-match however was incompatible.

The incompatible group had no combination where there was an Rh (D) positive baby and an Rh (D) negative mother. There were 7 such combinations in the ABO compatible group. One was considered separately because of the obvious sensitization. If the other 6 are removed from the ABO compatible group and the remaining 56 cases considered separately, the results are even more dramatic as recorded in Table II.

TABLE II

TYPE COMBINATION	NO. OF CASES	RANGE (MG. %)	AVERAGE (MG. %)
1. ABO compatible with no potential Rh (D) incompatibility	56	150 to 425	276
2. ABO compatible with potential Rh (D) incompatibility	6	195 to 350	254
3. Type B heterospecific pregnancy with negative Coombs test	11	110 to 315	221
4. Type A heterospecific pregnancy with negative Coombs test	12	165 to 295	217
5. Positive Coombs test	2	165	165

Comment

The wide variation in apparently normal fibrinogen levels makes any significant data very difficult to obtain. Pritchard and Ratnoff[14] found the range in 36 nonpregnant women to be 164 to 485 mg. per cent with an average of 294 mg. per cent. The variation seems to be over an even wider range during pregnancy.[1] Although other authors[8, 9] reported considerably higher levels during pregnancy, our experience did not confirm this. The blood in this series, however, was obtained after the first stage of labor and a drop is thought to occur during labor. Since the same technique[19] was used in all cases the error if any would be relative.

The few low results in the compatible pregnancies seem to indicate that although incompatibility may contribute to hypofibrinogenemia or even be a cause in some cases, it certainly is not the only etiological factor in this condition. With many low results in the clinic patients, it is our intention to determine the role of nutrition. There are also known cases of congenital hypofibrinogenemia. Despite the care taken in ruling out incompatibility, it is plausible that some incompatibility eludes detection by our usual laboratory methods, and this too must be considered as a cause of some low results

in the compatible group. Likewise, one might expect some high results in the incompatible cases. Some start at a normally higher level before pregnancy. Incompatibility cannot be implicated unless fetal antigen enters the maternal circulation. A certain percentage of infants are not secretors. A study which would correlate various factors, such as fibrinogen levels before pregnancy, during pregnancy, before labor, before delivery, after delivery of the placenta, and during the postpartum period, as related to such factors as amount of fetal blood in the maternal circulation, blood types, level of blood antibody titers, and whether or not the fetus is a secretor, would help clarify this problem. A good deal of work needs to be done, because most studies involve clinical cases of hypofibrinogenemia, or cases with complications ordinarily associated with hypofibrinogenemia. A search of the literature has failed to discover any extensive study of normal patterns in the changes of fibrinogen level during pregnancy and the postpartum period that takes heterospecific pregnancies into consideration.

Summary and Conclusions

1. Fibrinogen levels were obtained in 87 mothers approximately 5 minutes before delivery.

2. The highest fibrinogen levels were obtained in pregnancies homospecific for A and B factors. Lower levels were noted in pregnancies heterospecific for A and B or in cases with clinical erythroblastosis.

3. The gradation of effect seemed to be comparable to findings previously noted in the problem of erythroblastosis or in the administration of blood transfusions. Rh heterospecificity without sensitization had the least effect, ABO heterospecificity had more effect, and the lowest results occurred in the presence of a positive Coombs test.

4. Blood incompatibility between the fetal and maternal blood is a contributing factor in cases of hypofibrinogenemia and can cause subclinical lowering of the fibrinogen in some apparently otherwise normal pregnancies.

We wish to thank the individual members of the Obstetrical staff of the Paterson General Hospital who aided in this study by supplying blood specimens from their private patients, and also the Department of Anesthesia for their cooperation. In addition, we wish to thank Miss Irene R. Reilly and Miss Frances E. Orr, both from the Maple Medical Laboratory in Ridgewood, New Jersey, for performing all the laboratory procedures without financial remuneration.

The antisera were supplied by the Knickerbocker Foundation, Inc., New York.

References

1. Bowman, H. S., and Yelito, M. B.: Am. J. Obst. & Gynec. 74: 670, 1957.
2. Bromberg, Y. M., Salzberger, M., and Abrahamov, A.: Am. J. Obst. & Gynec. 74: 674, 1957.
3. Bromberg, Y. M., Salzberger, M., and Abrahamov, A.: Obst. & Gynec. 7: 672, 1956.
4. Davidsohn, I.: Obst. & Gynec. 8: 318, 1956.
5. Frick, P. G., and McKelvey, J. L.: Am. J. Obst. & Gynec. 70: 328, 1955.
6. Hartmann, R. C., and McGanity, William J.: Obst. & Gynec. 9: 466, 1957.
7. Hodgkinson, C. P., Margulis, R. R., and Luzadre, J. H.: J. A. M. A. 154: 557, 1954.
8. Kennan, A. L., and Bell, W. N.: Am. J. Obst. & Gynec. 73: 57, 1957.
9. Kinch, R. A. H.: Am. J. Obst. & Gynec. 71: 746, 1956.

10. Page, E. W., Fulton, L. D., and Glendening, M. B.: AM. J. OBST. & GYNEC. 61, 1116, 1951.
11. Paxson, N. F., O'Riordan, J. P., Gollub, S., Alpizar, S., and Riesz, P. B.: AM. J. OBST. & GYNEC. 75: 618, 1958.
12. Potter, E. L.: Rh: Its Relation to Congenital Hemolytic Disease, Chicago, 1947, The Year Book Publishers, Inc.
13. Pritchard, J. A.: AM. J. OBST. & GYNEC. 72: 946, 1956.
14. Pritchard, J. A., and Ratnoff, O. D.: Surg. Gynec. & Obst. 101: 467, 1955.
15. Reid, D. E., Weiner, A. E., and Roby, C. C.: AM. J. OBST. & GYNEC. 66: 465, 1953.
16. Reid, D. E., Weiner, A. E., Roby, C. C., and Diamond, L. K.: AM. J. OBST. & GYNEC. 66: 500, 1953.
17. Stouffer, J. G., and Ashworth, C. T.: AM. J. OBST. & GYNEC. 75: 407, 1958.
18. Weiner, A. E., Reid, D. E., and Roby, C. C.: AM. J. OBST. & GYNEC. 66: 475, 1953.
19. Fister, H. J.: Manual of Standard Procedures for Spectrophotometric Chemistry, New York, 1950, Standard Scientific Supply Corp., Publisher.

HYPOFIBRINOGENEMIA

Report of a Case Managed by Cesarean Hysterectomy

CARLTON N. ADAMS, M.D., AND SAM J. CRAWLEY, M.D.,*
WINSTON-SALEM, N. C.

(From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital)

FOR more than fifty years it has been observed that hemorrhage from the uterus and other sites may result from clotting defects associated with various complications of pregnancy.[1, 2] It was not until 1936, however, that a decrease in blood fibrinogen was first implicated as the causative factor in such cases.[3] Moloney, Egan, and Gorman[4] were the first to employ fibrinogen replacement as a method of treating these patients.

Among the obstetric conditions which may cause the plasma fibrinogen to fall to hemorrhagic levels are abruptio placentae, amniotic fluid embolism, retained dead fetus, and severe toxemia. The mechanism responsible for the decrease in fibrinogen is not yet fully understood. The most commonly accepted theory supposes that the fibrinogen in the maternal bloodstream is converted to fibrin by thromboplastin liberated from the placenta and decidua.[4-10] Another theory is that placental or uterine fibrinolysinokinase activates the maternal fibrinolytic system, leading to destruction of fibrinogen and fibrin.[5, 11, 12, 13] A third possibility is that sufficient fibrin is deposited in the intervillous spaces of the placenta, or at the placental site in the case of abruptio placentae, to deplete the plasma of fibrinogen.[14]

In the case to be reported, hypofibrinogenemia was associated with a retained dead fetus in an Rh-negative patient.

The patient was a 37-year-old married woman, gravida iv, para i, abortions 0, stillbirths 2. The patient was Rh negative, her husband Rh positive.

The first pregnancy produced a normal, full-term infant, after an uneventful prenatal course, labor, and delivery. The second pregnancy ended in the birth of a 3 pound stillborn infant near term. The fetus had been dead for 6 weeks prior to delivery. One month post partum there was a uterine hemorrhage requiring 1,000 c.c. of whole blood and a dilatation and curettage. The third pregnancy produced a 6 pound stillborn infant at 35 weeks; fetal death had occurred at 28 weeks. With this pregnancy, the patient had slight vaginal bleeding for one week ante partum, followed by the spontaneous onset of labor and a spontaneous vaginal delivery without difficulty. A severe hemorrhage occurred immediately after delivery, however, necessitating transfusion of 2,500 c.c. of whole blood and a dilatation and curettage.

*Present address, Boiling Springs, N. C.

In her fourth pregnancy (the only one in which she came under our observation) the patient did well until 26½ weeks, at which time fetal movements disappeared. When she was seen at the twenty-eighth week, no fetal heart sounds were heard. One week later she had lost 2¾ pounds, and the blood pressure had risen from 140/80 to 150/90. She was admitted to the hospital, where Pitocin was administered in an unsuccessful attempt to induce labor. The patient was discharged the following day in good condition.

On Oct. 20, 1957—7 weeks after the death of the fetus—we began performing serial fibrinogen titers,* using a modification† of the method of Bowman and Yelito.[15] The results are shown in Table I. On the morning of November 15 the patient awoke to find a large spot of blood on her pillow, and noted that her gums were bleeding. She was admitted to the hospital that day for observation and preparation for definitive treatment. On November 18 the fibrinogen titer was 1:1, and the patient's blood failed to clot. (This was before operation and before fibrinogen administration.) Four cubic centimeters of plasma from this sample was taken and to this was added 40 mg. of fibrinogen. A firm fibrin clot was formed and remained stable after incubation at 32° C. for 72 hours, an indication that the patient's plasma contained no significant amounts of a fibrinolytic substance.

TABLE I. SERIAL FIBRINOGEN LEVELS COMPARED WITH THE QUANTITATIVE FIBRINOGEN AND CLOT OBSERVATION TESTS

DATE	TITER	QUANTITATIVE FIBRINOGEN (PER 100 C.C. OF BLOOD)	CLOT LYSIS
10/20/57	1:100		
10/30/57	1:50		
11/ 6/57	1:50		
11/13/57	1:20		
11/15/57	1:20		90 minutes
11/16/57	1:10	80 mg.	30 minutes
11/18/57	1:1*	72 mg.	Blood failed to clot
11/19/57	1:100†	319 mg.	Stable after 72 hours

*Before operation and before fibrinogen administration.
†Twenty-four hours after administration of second unit of fibrinogen.

On the morning of November 18, immediately after the patient had received 2.2 Gm. of fibrinogen intravenously, a cesarean hysterectomy was performed, with removal of the uterus and its contents in toto. Although no unusual bleeding was noted during the procedure, about 200 c.c. of semiclotted blood was seen on the operating table and in the vagina upon completion of the operation, and the anesthesiologist reported slight bleeding from the gums. Inspection of the vagina with the patient in stirrups showed active bleeding from the vaginal cuff. Attempts to suture the cuff were futile, as new bleeding seemed to arise from the site of each needle puncture. Clamps were left in place, but oozing continued for 3 hours after operation, until the patient was given another 2.2 Gm. of fibrinogen. Bleeding then ceased almost immediately.

Fifteen hundred cubic centimeters of whole blood was given during and following the operation, and the patient was given another 500 c.c. on the third postoperative day, when the hemoglobin was 7.8 Gm. From the third through the fifth postoperative day her temperature was elevated, ranging between 100.4° and 101° F. orally, but her course was otherwise smooth. When the skin sutures were removed on the seventh postoperative day, there was evidence of previous bleeding about the operative site. She was discharged on the ninth postoperative day in good condition, with a hemoglobin determination of 11 Gm.

*Fibrinogen was supplied by Roy Muse of the Ortho Pharmaceutical Corporation.
†While we use the dilutions of plasma recommended by Bowman and Yelito, we find that interpretation is made easier if the final volume in each tube is kept constant.

Comment

Hypofibrinogenemia should be suspected whenever a pregnant patient bleeds subcutaneously or from the mucous membranes, and in every pregnancy complicated by one of the conditions known to be associated with decreased plasma fibrinogen. Surgical shock also and other as yet unknown conditions may lead to depletion of blood fibrinogen.[16] The diagnosis can be made by one of three laboratory tests: quantitative fibrinogen determination, the clot observation test, and determination of the fibrinogen titer.

Quantitative fibrinogen determinations are not generally available, and are still too cumbersome for routine clinical application. The simple, time-honored clot observation test is valuable, and in our case gave results which closely paralleled those obtained by the titer method. This test has two disadvantages, however: (1) when fibrinogen values are only moderately decreased, several hours are required for the deficiency to become apparent; and (2) the test does not make it possible to distinguish between lack of fibrinogen and an inadequate supply of other clotting factors. The advantages of determining the fibrinogen titer by the method of Bowman and Yelito[15] are: (1) this method is specific for fibrinogen deficiency; (2) it is sufficiently accurate for clinical use; (3) the result can be determined almost immediately; and (4) it can be performed without special apparatus and by untrained personnel.

It is not known what percentage of patients with retained dead fetus have coagulation defects. Pritchard and Ratnoff[17] found significant hypofibrinogenemia in 8 out of 30 patients who retained dead fetuses for 5 weeks or longer. No case of significant hypofibrinogenemia has been reported earlier than the fifth week after fetal death.[17] In patients with a retained dead fetus, determinations of the fibrinogen titer should be made weekly or biweekly, beginning at the third or fourth week after fetal death.

A study of the reported cases of afibrinogenemia and hypofibrinogenemia[4, 5, 11, 13, 17, 18] reveals certain facts which have clinical application:

1. Serious bleeding rarely occurs before the onset of labor, no matter how low the fibrinogen level falls.
2. Many patients with severe fibrinogen destruction have had some manipulative procedure such as manual removal of the placenta, prolonged vigorous massage of the uterus, uterine pack, hysterotomy, or cesarean section. Presumably, these procedures cause the exaggerated release of some noxious agent, whether it be thromboplastin, fibrinolysin, or some unknown factor. Pritchard[19] has reported that in a small number of cases normal labor had no deleterious effect on the plasma fibrinogen.
3. In almost all the fatal cases of afibrinogenemia, regardless of the final pathologic diagnosis (lower nephron nephrosis, Waterhouse-Friderichsen syndrome, rupture of the liver, and so forth), the patient had had a prolonged period of hypotension due to uterine hemorrhage.
4. When hysterectomy was performed before the patient's condition had deteriorated seriously, uniformly good results were obtained.
5. A large percentage of patients with the dead fetus syndrome are Rh negative and are isosensitized to the Rh factor. If the husband of such a patient is homozygous in respect to the Rh factor, the chance of future successful pregnancies is practically nil. Preservation of the childbearing function in these patients subjects the mother to needless hazards.

One approach to the treatment of hypofibrinogenemia is by replacement therapy. While the milder cases may be cured by prompt termination of the pregnancy alone,[17] most patients should receive purified fibrinogen supplemented by whole blood. Bank blood is satisfactory, although it was formerly

thought that fresh blood was necessary.[20] Blood becomes incoagulable when the plasma fibrinogen level falls below 100 mg. per 100 c.c.[17, 18] (3 Gm. of total plasma fibrinogen). Donor blood can be expected to supply around 0.75 Gm. of fibrinogen per 500 c.c. Theoretically, a patient with depleted fibrinogen would require 3 Gm. of fibrinogen or 2,000 c.c. of whole blood (allowing for dilution of the donor blood) to make the blood clot. In practice, however, this amount is frequently inadequate, since many patients have required 12 to 15 Gm. of fibrinogen to render the blood coagulable.[20-24] If hemorrhage and defibrination are allowed to continue, replacement therapy alone will not prevent a fatal outcome. The plasma fibrinogen can be restored to normal only by termination of the pregnancy, or in some severe cases by removal of the uterus.[21, 25]

Since the administration of fibrinogen is not without danger,[26] we attempted to give the minimum amount necessary to achieve hemostasis in our patient. In retrospect, the absolute minimum to achieve this end probably closely paralleled the theoretically calculated amount of 3 Gm.

While some authors[5, 27] contend that hysterectomy is rarely, if ever, indicated in the treatment of afibrinogenemia, we felt that, for several reasons, cesarean hysterectomy was the treatment of choice in this case. Removing the uterus eliminates not only the source of thromboplastins, but also the usual source of serious hemorrhage. Even in the presence of a severe coagulation defect, bleeding from cut surfaces where major blood vessels are ligated (as in cesarean hysterectomy) is less severe than bleeding from the vascular postpartum uterus. Furthermore, since genetic studies had showed the patient's husband to be homozygous with respect to the Rh factor, sterilization of the patient seemed highly desirable.

Sandberg[28] has recently reported favorable experience with cesarean hysterectomy, rather than cesarean section combined with tubal ligation. He pointed out that this method eliminates sterilization failures and the subsequent development of either abnormal bleeding or uterine carcinoma.

It is our belief that cesarean hysterectomy should be considered more often in the management of cases of hypofibrinogenemia in pregnancy.

Summary

1. A case of hypofibrinogenemia associated with a retained dead fetus is reported.

2. The value of a simple diagnostic (and prognostic) procedure in the management of the incoagulable blood syndrome is discussed.

3. Cesarean hysterectomy is recommended as the treatment of choice in certain cases of hypofibrinogenemia associated with pregnancy.

References

1. DeLee, J. B.: Am. J. Obst. 44: 785, 1901.
2. Willson, P.: Surg. Gynec. & Obst. 34: 57, 1922.
3. Dieckmann, W. J.: Am. J. Obst. & Gynec. 31: 734, 1936.
4. Moloney, W. C., Egan, W. J., and Gorman, A. J.: New England J. Med. 240: 596, 1949.
5. Page, E. W., Fulton, L. D., and Glendening, M. B.: Am. J. Obst. & Gynec. 61: 1116, 1951.
6. Schneider, C. L.: Am. J. Physiol. 149: 123, 1947.
7. Schneider, C. L.: Surg. Gynec. & Obst. 90: 613, 1950.
8. Schneider, C. L.: Surg. Gynec. & Obst. 92: 27, 1951.
9. Ratnoff, O. D., Pritchard, J. A., and Colopy, J. E.: New England J. Med. 253: 63, 1955.
10. Frick, P. G., and McKelvey, J. L.: Am. J. Obst. & Gynec. 70: 328, 1955.
11. Lewis, J. H., Leary, D. C., Fresh, J. W., and Ferguson, J. H.: Am. J. Obst. & Gynec. 75: 418, 1958.

12. Phillips, L. L., Butler, B. C., and Taylor, H. C., Jr.: Am. J. Obst. & Gynec. 71: 342, 1956.
13. Weiner, A. E., Reid, D. E., and Roby, C. C.: Am. J. Obst. & Gynec. 60: 379, 1950.
14. Stouffer, J. G., and Ashworth, C. T.: Am. J. Obst. & Gynec. 75: 407, 1958.
15. Bowman, H., and Yelito, M.: Am. J. Obst. & Gynec. 74: 670, 1957.
16. Klein, M., Biskind, J. I., and Silverberg, A.: Am. J. Obst. & Gynec. 71: 51, 1956.
17. Pritchard, J. A., and Ratnoff, O. D.: Surg. Gynec. & Obst. 101: 467, 1955.
18. Reid, D. E., Weiner, A. E., Roby, C. C., and Diamond, L. K.: Am. J. Obst. & Gynec. 66: 500, 1953.
19. Pritchard, J. A.: Am. J. Obst. & Gynec. 72: 946, 1956.
20. Rosenfeld, L., and Shinowara, G. Y.: J. Lab. & Clin. Med. 37: 311, 1951.
21. Heaton, S. C., Solomon, C., and Happel, E.: Am. J. Obst. & Gynec. 70: 320, 1955.
22. Peckham, C. H., Jr., and Middlebrook, L. F., Jr.: Am. J. Obst. & Gynec. 65: 644, 1953.
23. Hodgkinson, C. P., Margulis, R. R., and Luzadre, J. H.: J. A. M. A. 154: 557, 1954.
24. Sawitsky, A., Leahy, D. J., and Carpenter, F.: Am. J. Obst. & Gynec. 67: 349, 1954.
25. Charles, D.: Obst. & Gynec. 10: 161, 1957.
26. Rettew, P. L., Meharg, G., and Brubaker, E. R.: Obst. & Gynec. 10: 169, 1957.
27. Murphy, C. J., Jr., Picot, H., and Thompson, G. H.: Am. J. Obst. & Gynec. 72: 1197, 1956.
28. Sandberg, E. C.: Obst. & Gynec. 11: 59, 1958.

OXYTOCIC EFFECTS OF INTRAVENOUSLY ADMINISTERED HYPERTONIC SODIUM CHLORIDE IN HUMAN PREGNANCY AT TERM*†

CHARLES H. HENDRICKS, M.D., AND TOBEY HELFAND, M.D.,**
CLEVELAND, OHIO, AND ROBERTO CALDEYRO-BARCIA, M.D.,
MONTEVIDEO, URUGUAY

(From the Department of Obstetrics and Gynecology, Western Reserve University School of Medicine)

IT HAS been established that the injection of hypertonic solutions into the blood stream will result in antidiuresis.[1] The mechanism of action, according to Verney,[2] is probably the following: an increase in osmotic pressure in the carotid blood serves as a stimulus to osmoreceptors located in the anterior hypothalamic region, bringing about a discharge of antidiuretic hormone (ADH) from the neurohypophysis. Working with dogs, Abrahams and Pickford[3] found that hypertonic saline injections would induce not only antidiuresis but also would increase uterine activity.

The present study was designed to test whether or not injections of hypertonic saline would cause demonstrable oxytocic effects in pregnant human subjects. A related report was published by de Bruine,[4] who employed hypertonic saline to combat uterine inertia.

Material and Methods

A total of 14 pregnant women, all in late pregnancy, served as subjects for the study.

The subject was first hydrated orally and/or intravenously until a diuresis was established. Then approximately 20 Gm. of NaCl (either 800 c.c. of 2½ per cent solution or 400 c.c. of 5 per cent solution) was administered intravenously over a 25 to 30 minute period. An indwelling catheter was set in place, and the bladder carefully drained every 15 minutes, the output being recorded. In the early cases, uterine activity was followed by a record of the observer's estimations of the interval, duration, and intensity of contractions. In later cases, an externally recording tokodynamometer was available for making a record of uterine activity. In the final case, more precise methods were employed, as will be described.

*This work was supported in part by a research grant (H-1914) from the National Heart Institute of the National Institutes of Health, Public Health Service.

†The final part of this work was done at the Sección Fisiología Obstétrica, University of Montevideo, Uruguay, where Dr. Caldeyro-Barcia is codirector of the laboratories, and where Dr. Hendricks' visit was made possible through a fellowship grant from the Josiah Macy, Jr., Foundation.

**Dr. Helfand participated in the study during 1955 in partial fulfillment of the requirements of the Project Teaching Program of the Medical Curriculum, Western Reserve University School of Medicine.

TABLE I. EFFECT OF INTRAVENOUSLY ADMINISTERED HYPERTONIC SALINE ON UTERINE CONTRACTILITY

CASE NO.	PARITY	WEEKS' GASTATION	CONDITION BEFORE INFUSION	EFFECT OF INFUSION	SUBSEQUENT COURSE
1	ii	38	Threatening labor	Definite increase in duration and painfulness of contractions	Contractions gradually subsided. Next day labor easily induced
2	ii	42	Irregular contractions every 8-10 minutes	Contractions increased to every 2-3 minutes. Some pain	Contractions ceased. Next day spontaneous rapid labor
3	0	40	Few ineffective contractions	Hard labor ½ hour after infusion completed	Delivery 4 hours post infusion
4	0	40	Threatened labor for 10 hours. No dilatation	Hard contractions every 2 minutes by end of infusion	Complete dilatation 1½ hours post infusion
5	vi	40	Few Braxton-Hicks contractions	Mild increase in contractions	Onset of good labor spontaneously at 13 hours post infusion
6	ii	41	No labor	Several mild-to-moderate contractions post infusion	Spontaneous onset of labor 5 days later
7	ii	40	Fleeting contractions but 3 cm. cervix dilated	Moderate contractions from end of infusion. Labor began	Delivery 2½ hours post infusion
8	0	36	Equivocal labor 12 hours. Much pain	No demonstrable change	Went home. Was delivered 2 days later
9	0	42	Not in labor	Painful, more frequent contractions post infusion. Intravenous Pitocin drip caused same effect	Next day another intravenous Pitocin drip failed to induce labor
10	i	41	Not in labor	Slow onset of progressively improving contractions	Delivery 11 hours post infusion
11	ii	37	False labor, 1 day	Excellent contractions	Delivery 7 hours post infusion
12	ix	27	Not in labor	Excellent contractions	Delivery 3½ hours post infusion
13	0	40	Not in labor	No significant increase in contractions	Intravenous Pitocin caused "pit. contractions." Active labor after rupture of membranes
14	0	40	Not in labor. Under study with intermittent infusion of oxytocin	Definite increase of contractions	Contractions subsided. See Fig. 1

The infusions were quite well tolerated, the only consistent side reaction being a complaint of intense thirst, which usually began after about 10 minutes of the infusion, regardless of how well the patient had been hydrated. Other, less commonly observed phenomena were a feeling of chilliness during the late

portion of the infusion, and a sensation of nasal congestion. One subject complained of a headache for a short period of time. One other subject had a transient but rather alarming hypertension, the pressure rising momentarily as high as 170/100, but returning to normotensive levels 10 minutes after the infusion was discontinued.

Results

Antidiuresis was present in all cases observed, beginning either during the later part of the infusion time or else within one-half hour after the completion of the infusion. The antidiuresis was prolonged, lasting in some instances up to 4 hours.

The uterine reactions were variable, but some degree of response was observed in 12 out of the 14 cases (Table I). In 5 cases, there was good evidence that labor was either induced or enhanced. In 4 other cases, uterine contractility definitely increased but then subsided prior to the onset of labor, while in 3 cases there was only a mild and transient increase in contractility. The remaining 2 subjects showed no demonstrable increase in contractility by the measuring methods then available.

The following 3 cases are representative of those tabulated:

Good oxytocic effect. Case 3, a 34-year-old primigravida at term, was hospitalized on Nov. 29, 1953, because of bloody discharge and intermittent contractions. The cervix was 2 cm. dilated, as it had been for the previous 2 weeks. During the first 8 hours after admittance, there were only a few ineffective contractions. Seven hundred cubic centimeters of 2½ per cent NaCl were then given intravenously during a 32 minute period. A marked antidiuresis ensued, and 30 minutes after the completion of the infusion there were good contractions at 2½ minute intervals. Cervical dilatation was complete 3 hours post infusion, and the subsequent delivery of a normal male infant was uneventful.

"Pitocin-like" contractions without effective labor. Case 1, a 28-year-old para iii, gravida iv, 38 weeks pregnant, Rh sensitized, was hospitalized on Nov. 22, 1953. After 11 hours of mild, intermittent, ineffective contractions, 600 c.c. of 2½ per cent NaCl was given intravenously over a 35 minute period. The subject had been previously hydrated. During the infusion the urinary output dropped to less than 10 per cent of its maximum diuresis (11.6 c.c. per minute to 1.1 c.c. per minute) and the output averaged less than 1 c.c. per minute during the ensuing 4 hours, after which it gradually increased. During the 4 hours post infusion (i.e., during the period of antidiuresis), the contractions became noticably more intense, more painful, and more frequent. Labor failed to proceed, however, the cervix remaining at 2 cm. dilatation and 0 station, and the contractions gradually subsided. The next day, the membranes were artificially ruptured and, with a few drops of 1:1,000 Pitocin solution intravenously, labor was easily established and completed, a normal infant being delivered uneventfully.

Minimal evidence of oxytocic effect. Case 6, a 28-year-old para ii, gravida iv, 10 days post term, was hospitalized for induction of labor on March 9, 1954. The subject was having no contractions of which she was aware, and the cervix, though not dilated, was fairly well softened. No significant contractions were palpated during a 1 hour observation period prior to the infusion. An infusion of 850 c.c. of 2½ per cent NaCl was administered intravenously during a 25 minute period, and at the end of this time the first mild contraction was palpable. There were several further mild contractions following this at intervals of 8 to 12 minutes, lasting 70-80 seconds; the subject was aware of these contractions only as a "feeling of tightness" in the abdomen. There were 6 of these contractions during 40 minutes post infusion. One hour post infusion, 1 minim of Pitocin was given intramuscularly, which resulted in a short period of contractions of the same general type but at more frequent intervals. Because the subject did not appear to be particularly "inducible," she was discharged to await labor. She returned 5 days later in spontaneous rapid labor, and was delivered uneventfully.

It is a matter of additional interest to compare the response to Pitocin infusions to that brought about by the hypertonic saline. In Case 9, for example (at 42 weeks' gestation) the hypertonic NaCl brought about painful, more frequent contractions, which gradually subsided. Later in the day, an infusion of dilute Pitocin gave an almost identical result. The following day, a further infusion of Pitocin still failed to induce immediate active labor, but after a further 24 hours of slowly increasing activity a 4,800 gram male infant was delivered by low forceps. In Case 13, however, while hypertonic saline did not result in any demonstrable increase in contractility, a dilute Pitocin drip did result in painful contractions, which subsided when the drip was discontinued. Labor became established only after rupture of the membranes and further treatment with dilute intravenous Pitocin. Although the 1:1,000 Pitocin drip brought about more activity than did the hypertonic saline, it should be pointed out that the drip was being run at the rate of 20 drops per minute, a rate which appears to be substantially in excess of the oxytocic response which the hypertonic saline is capable of producing (Fig. 2).

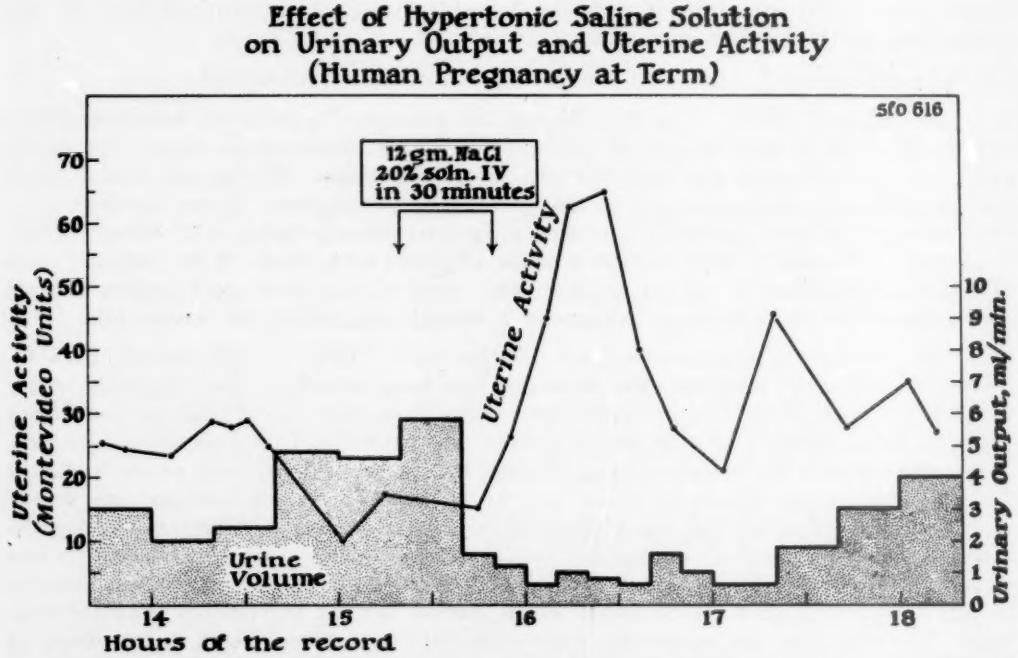


Fig. 1.—Showing how the intravenous administration of hypertonic NaCl in a previously hydrated patient brought about simultaneously both antidiuresis and a marked increase in uterine contractility.

If the object of this study were simply to find an effective method for the induction of labor through stimulation of the neurohypophysis, this series would be not at all impressive. The actual purpose of the study, however, was to try to demonstrate oxytocic effects, i.e., "the induction of contractions," and in this instance delivery was not an essential end point in the experiment.

It appears that infusions of the hypertonic solutions did in fact bring about the "induction of contractions," but that the amount of oxytocic factor(s) was equivalent to only small doses of Pitocin. It seems that in almost every case the infusion *did* enhance the uterine contractility: the total effect which appeared, however, was dependent upon the uterine "readiness to labor." This fits in with the observation that as the time for labor approaches the uterus becomes progressively more sensitive to oxytocic products.[5]

Accepting for the moment the concept that the uterus is in this sense only an end organ for the bioassay of potentially oxytocin-releasing stimuli, the case illustrated in Fig. 1 is particularly illuminating. The subject, a primigravida at term, was being studied during the induction of labor. Hydration was carried out until a fair diuresis was under way. Then, during a 30 minute period, 12 Gm. of NaCl was given intravenously in a 20 per cent solution by constant infusion. By the end of the infusion the urinary minute volume had dropped to about one-fifth the previous level, and the output remained low for nearly 2 hours. Coincidentally with the appearance of antidiuresis, the uterine activity, which had been in the neighborhood of 20 Montevideo units.[5] began a steady climb, reaching a peak of nearly 70 Montevideo units during the ensuing 40 minutes. Following this, the uterine activity again began to decline, tending to decrease more or less coincidentally in time with the release of the antidiuresis.

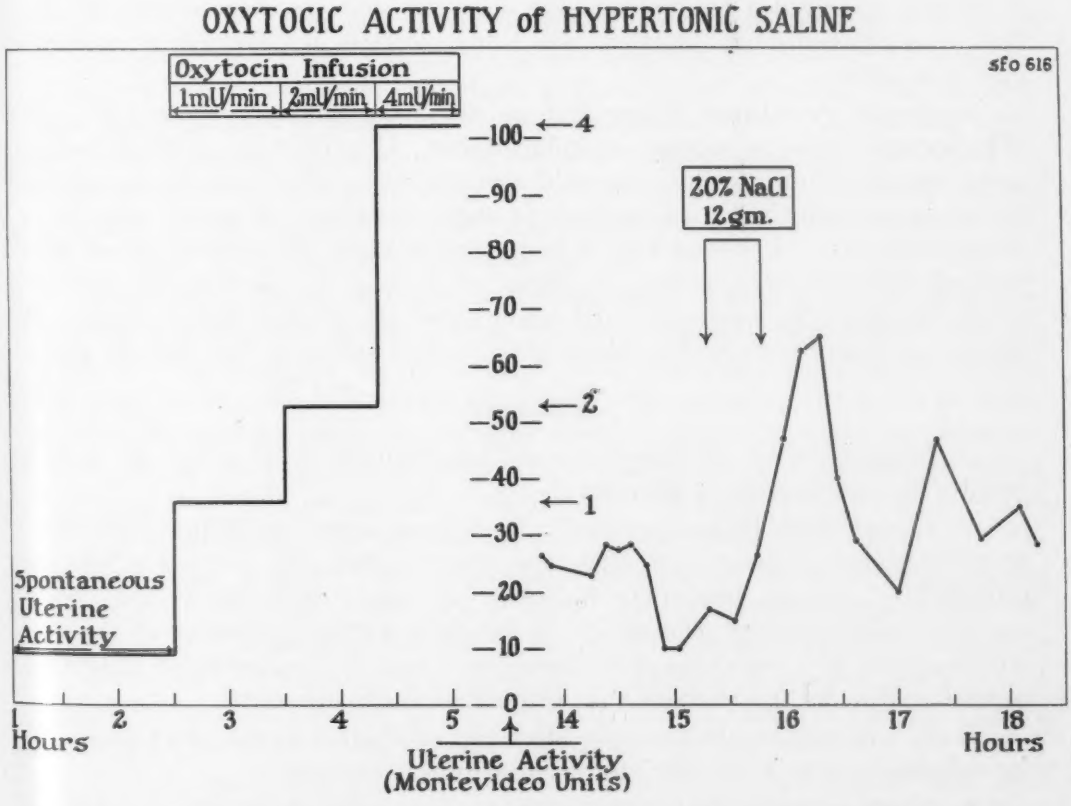


Fig. 2.—A comparison in the same subject between (a) the uterine activity induced by various rates of oxytocin infusion, and (b) the activity induced by the infusion of hypertonic saline. In this case, the transient increase in activity after hypertonic saline was somewhat greater than that produced by 2 mU per minute of synthetic oxytocin.

In this subject, previous observations had been carried out on the spontaneous uterine activity, that is, on the activity present in the absence of any sort of infusion. There had also been observations on the amount of uterine activity produced by the infusion of synthetic oxytocin at various rates. It may be seen from the graph (Fig. 2) that the maximum oxytocic effect of the hypertonic saline infusion was roughly equivalent to the effect of infusion of oxytocin within the range of 2 to 4 mU per minute.

Comment

There is little doubt that hypertonic saline increases uterine activity through its action upon the neurohypothalamic system. But some uncertainty remains regarding the identity of the products(s) which bring about the oxytocic effect. It has been shown that hypertonic saline brings about both antidiuretic and oxytocic effects. But the antidiuretic hormone has not only an antidiuretic effect but also an oxytocic effect.[1] Therefore there is the possibility that all the observed changes may be due to the antidiuretic hormone. On the other hand, it seems equally possible that the stimulation which releases ADH may also release oxytocin—the neurohypophysis being "flushed out" by the stimulus. Abrahams and Pickford[3] found that the antidiuretic response to hypertonic saline was equivalent to the action of 3 mU of Pitressin, but that 80-100 mU of Pitocin was needed to duplicate the observed oxytocic effect on the uterus. Thus they concluded that oxytocin was being secreted in even greater amounts than was ADH.

It should go without saying that we are not seriously proposing the use of hypertonic saline to enhance or induce labor. Unpredictable clinical results, unwarranted sodium loading, the mild systemic discomfort, and the occasional hypertension resulting from such a procedure combine to make this—as a therapeutic agent—a clumsy tool at best. Fortunately, the availability of both purified and synthetic oxytocic products, which may be administered intravenously in carefully controlled and maintained physiologic dosage, makes it totally unnecessary to consider the use of hypertonic saline as a therapeutic agent.

Summary

1. Administration of hypertonic sodium chloride to 14 pregnant women resulted in antidiuresis in all cases.

2. The oxytocic response varied. In 5 cases there was definite induction or enhancement of labor, in 4 cases there was demonstrable increase in uterine contractility without immediate induction of labor, while in 3 cases there was only mild transient increase in the intensity and/or frequency of the contractions. In the remaining 2 subjects there was no demonstrated alteration in contractility by the methods then available for measurement.

3. In one subject, the oxytocic effect was equivalent to the effect produced by infusion of 2 to 4 mU per minute of synthetic oxytocin.

4. Whether the oxytocic effect of hypertonic solutions is due to ADH or some combination of ADH and oxytocin in unknown at this time.

We would like to express our thanks to Dr. Jerold M. Rosenblum, who assisted in several of the earlier case studies which were performed at University Hospital, Columbus, Ohio, in 1953-1954.

References

1. Harris, G. W.: Neural Control of the Pituitary Gland, London, 1955, Edward Arnold, Ltd.
2. Verney, E. B.: Lancet 2: 1295, 1957.
3. Abrahams, V. C., and Pickford, M.: J. Physiol. 122: 56P, 1953.
4. de Bruine, T. L. A.: Bull. Soc. royale belge de gynéc. et obst. 27: 414, 1957.
5. Caldeyro-Barcia, R., et al.: J. Pharmacol. & Exper. Therap. 121: 18, 1957.

OLD AND NEW METHODS FOR INDUCTION OF LABOR AND OF PREMATURE LABOR*

W. C. W. Nixon, M.D. (London), F.R.C.S. (England), F.R.C.O.G., and C. N. Smyth, M.A., B.M. (Oxon), M.I.E.E., London, England

(From the Obstetric Unit, University College Hospital)

INDUCTION of labor for pelvic deformity was mentioned by Soranus of Ephesus in the second century A.D., but there is no evidence to show the extent to which induction—as apart from artificial abortion—was actually carried out in ancient times. Both Ambroïse Paré (1510-1590) and his pupil, Jacques Guillemeau, induced premature labor in cases of severe uterine hemorrhage, and Paré devised an instrument for dilating the cervix. Louise Bourgeois (1563-1636), the celebrated French midwife, is also said to have induced premature labor in women with contracted pelves.

The modern history of the operation dates from 1756 when George Macaulay, surgeon man-midwife to the British Lying-in Hospital, performed it on the wife of a linen draper in the Strand. This case was reported by Thomas Denman (1785) whose judicious advocacy of the operation led to its adoption in England long before it was accepted abroad. The only method of induction mentioned by Denman was puncture of the membranes, and this became widely known as the "English method." Scheel, of Copenhagen, whose name is also sometimes associated with the method, did not describe it until 1799.

Following Denman, the outstanding advocate of induction was Samuel Merriman (1771-1852); but many other British obstetricians—notably A. Hamilton, J. Ramsbotham, Blundell, Burns, Barnes, and Radford—helped to elaborate both indications and limitations. Thomas C. James, Professor of Obstetrics in the University of Pennsylvania, was in 1810 the first in America to induce premature labor. James's operation was carried out at the end of the seventh month in a patient with contracted pelvis; both mother and child survived. The first induction in Germany was in 1804; in France it was opposed by Baudelocque and Capuron and was not performed until 1831. The neglect of the operation abroad is shown by the fact that 72 of the 161 cases reported up to 1831 had been in England as reported by Fasbender in 1906.

James Hamilton, of Edinburgh, in 1810 suggested digital separation of the membranes from the lower segment and later, in 1836, described a method of rupturing the membranes at some distance from the external os by means of a catheter and stylet. His pupil Moir in 1851 used this method with success,

*Presented before the Obstetric and Gynecologic Assembly of Southern California, Feb. 13, 1958.

and it is essentially the method employed today with the Drew Smythe catheter for tapping the "hindwaters." Other methods of induction tried out in the early part of the nineteenth century included the use of electricity, suggested by Herder in 1802; massage of the breasts by Friedreich in 1839; vaginal and intrauterine injection of hot water, Cohen's method (1846). Krause's method introduced in 1853—the insertion of a bougie between the membranes and the uterine wall—remained in favor for many years. Induction by means of inflatable rubber bags introduced through the cervix also dates from the middle of the last century, the best known devices being the colpeurynter of Carl Braun (1851), the cervical dilators of Barnes (1861) and Tarnier (1862), and the metreurynter of Champetier de Ribes (1888).

In the early part of the present century induction was often done unnecessarily, and some British obstetricians deplored its use in primigravidas. In fact, in 1841 Ramsbotham was already teaching that the "induction of premature labour in the first pregnancy is not to be thought of." In 1920, B. P. Watson, now of New York, introduced a method of medical induction by means of castor oil, quinine, and repeated doses of pituitary extract, but this has not fulfilled its early promise. So far as the technique of induction is concerned, the earliest method—rupture of the membranes—has largely superseded its rivals. Drew Smythe (1931) of Bristol designed a silver catheter for puncturing the hindwaters. Once very popular, this instrument is no longer in use in many clinics for reasons which appear later in the text.

Indications

This article deals mainly with the methods of induction of labor, so a complete list of indications is not included. Common indications divided somewhat arbitrarily between maternal and fetal are:

1. Maternal.—Toxemias of pregnancy, essential hypertension, renal disease, and certain acute or chronic diseases complicating pregnancy, in some of which induction of labor is sometimes indicated; for example, heart disease, anemia, tuberculosis, diabetes mellitus, psychosis.

In acute illnesses such as pneumonia, influenza, malaria, typhoid, which are notorious for the high incidence of abortion and premature labor, it is safer to treat the disease along accepted lines rather than to interfere with the pregnancy.

Labor is also induced in the interest of the mother when the fetus is dead or grossly abnormal.

2. Fetal.—Induction of labor is performed in the interest of the fetus when its life would be jeopardized by the continuation of pregnancy. Under this heading are included postmaturity; previous dystocia due to an overlarge fetus; certain cases of rhesus isoimmunization; cephalopelvic disproportion; hydramnios; antepartum hemorrhage.

Of all the indications (Table I) enumerated above, toxemia of pregnancy, hypertension, and postmaturity are the most important. The subject of postmaturity is still controversial but many obstetricians are of the opinion that pregnancy should not be allowed to continue longer than 42 weeks. The research of Walker[24] has shown that after term the efficiency of the placenta starts to diminish and the fetus suffers increasingly from anoxia the longer it remains in utero. This is particularly marked when toxemia is combined with postmaturity.

TABLE I. INDICATIONS FOR SURGICAL INDUCTION OF LABOR, 1952 TO 1956, INCLUSIVE

INDICATION	NO.	%
Toxemia	297	35
Hypertension (essential)	188	22
Postmaturity	255	30
Miscellaneous (including pelvic disproportion)	116	13

Table II shows data relating to all the surgical inductions performed from 1952 to 1956, inclusive; during this period the induction rate was 12.7 per cent. It will be seen that the incidence of stillbirths and neonatal deaths in the induction group is lower than the total incidence in all deliveries.

TABLE II. DATA RELATING TO SURGICAL INDUCTION OF LABOR (AMNIOTOMY), 1952 TO 1956, INCLUSIVE

Total deliveries	6,729			
Total inductions	856 (12.7%)			
Induction-delivery interval (average)	25.7 hours			
	INCIDENCE AMONG INDUCTIONS		TOTAL INCIDENCE	
	NO.	%	NO.	%
Stillbirths	15*	1.8	130	1.9
Neonatal deaths	8	0.9	96	1.4
Genital sepsis	38	4.4	210	3.1
Cesarean sections	49	5.7	297	4.4

*Three died before induction and are included.

Methods of Induction

These are usually classified as surgical or medical, or a combination of both.

1. Surgical.—This includes rupture of the membranes (amniotomy) or the introduction of bougies, solid stomach tube, bags or balloons between the membranes and the lower uterine segment. "Sweeping the membranes" is a method some obstetricians favor in the presence of cephalopelvic disproportion or of breech presentation when it is felt better to conserve the forewaters. It should, of course, always be included in the operation of amniotomy.

Amniotomy: Puncture of the membranes began as a peculiarly British method of induction which is now coming into universal usage. Either the hind- or forewaters may be ruptured.

For high amniotomy Drew Smythe[20] devised an S-shaped silver catheter for introduction into the uterus above the presenting part with a stylet for puncturing the membranes. He claimed that by this method the forewaters were conserved and the risk of sepsis lessened. But there have been reports of accidents following the use of this instrument. One has personal knowledge of perforation of the uterus. Russell[13] has reported fatal fetal exsanguination following damage to fetal vessels in the placenta. Though fetal vessels may not be injured in the presence of placenta previa, the fetus may be jeopardized by further separation of the placenta. The incidence of sepsis is not reduced and the induction-labor interval is usually greater in high as compared with low amniotomy (see later data). Perhaps the only indication for high amniotomy is hydramnios or the case in which a sample of uncontaminated liquor is required for analysis (Rh isoimmunization).

Table III shows the effectiveness of low compared with high amniotomy. The times in hours are the averages for the inductions during 1956.

For low amniotomy (rupture of the forewaters) our procedure is as follows. The patient is admitted the night before, prepared, and given a sedative. The following morning she is admitted to the labor ward and given premedication (Demerol, 50 mg., and chlorpromazine, 12.5 mg., intramuscularly). Half an hour later she is placed in the lithotomy position and full aseptic and antiseptic precautions taken. The cervix is palpated and "typed" according to Cocks's[4] classification and its consistency is recorded; the station of the head is noted in relation to the ischial spines and the cervix; the fetal heart is checked.

The instrument used for rupturing the forewaters designed by Smyth[17] consists essentially of two small filelike surfaces on the slanting tip of a pair of curved forceps. As the forceps are closed these rough surfaces catch the membranes and bring them together in a fold cutting through it. The forceps succeed in doing this even when the membranes are closely applied to the head. Other features of the instrument are (1) a ratchet, so that the membranes can be held while the surgeon employs the guiding finger to ensure that they are suitably applied, (2) all parts of the forceps and handles are beveled off and spaced so that the forceps cannot pinch any part of the introitus, vagina, cervix, or the examining finger of the surgeon, (3) the filelike teeth are not deep enough to injure the fetus through the membranes.*

The membranes are widely and thoroughly separated from the lower uterine segment and the region of the internal os. The index finger of the left hand guides the tip of the forceps through the internal os. By an assistant pressing on the fundus or the presenting part, the pressure of the forewaters will be increased and rupture made easier. It is essential to remove plenty of liquor (about 500 ml.), pushing up the head slightly if fluid does not escape freely. This will result in the shortening of uterine muscle fibers and, by increasing the descent and pressure of the presenting part on the lower uterine segment and cervix, the main stimulus to the initiation of labor will be provoked. The fetal heart beat is recorded immediately after amniotomy and at quarter-hour intervals for the following hour. If the liquor is meconium-stained the fetal heart rate needs to be repeatedly observed and a decision reached as to whether cesarean section is indicated.

TABLE III. COMPARISON OF EFFECTIVENESS OF HIGH AND LOW AMNIOTOMY (TIMES IN HOURS)

	INDUCTION-DELIVERY INTERVAL		INDUCTION-ONSET OF LABOR INTERVAL		LENGTH OF FIRST STAGE	
INDICATIONS	HIGH	LOW	HIGH	LOW	HIGH	LOW
Primiparas.—						
Postmaturity	49	30	21	11	20½	14¼
Toxemia	40	18	19	3½	17	13¼
Multiparas.—						
Postmaturity	29	12	19	5½	9	6¼

2. Medical.—The time-honored ritual of castor oil, enema, hot bath with or without quinine, and intramuscular oxytocin, has fallen into disrepute. Not only was it usually a prolonged and uncomfortable ordeal but it was often useless and could be harmful to both mother and fetus. Moir[10] admirably sums up the position regarding medical induction: "I have long regarded medical induction before term as a waste of time, energy and suffering. W. J. Garrett working in my department in Oxford has reviewed 600 cases of induction of labour. Regarding medical induction, he found only 5 per cent successful (that is, labour starting within 24 hours) in patients before term. In contrast, 20

*The instrument can be obtained from Messrs. John Bell & Croyden Ltd., Wigmore Street, London, W.1.

per cent of medical inductions were successful after term. The addition of pituitary extract injections increased the success rates to 18 per cent and 35 per cent, respectively."

With retained dead fetus, quinine bihydrochloride (300 mg. at 4 hour intervals for three doses) is a useful addition to oxytocin. Similarly, estrogen, provided large doses are given, may assist oxytocin to stimulate the uterus to expel a dead fetus. These drugs are unreliable without oxytocin. Intravenous oxytocin infusion is the basis of the most certain and effective methods when surgical interference is contraindicated.

Blair Bell[2] introduced the use of posterior pituitary extract in obstetrics and described this in his monumental paper entitled "The Pituitary Body and Therapeutic Value of Infundibular Extract in Shock, Uterine Atony and Intestinal Paresis." Since that time much has been written on the use and abuse of oxytocic drugs in labor but Page[11] was the first to show the value of intravenous in preference to intramuscular oxytocin. In his article entitled

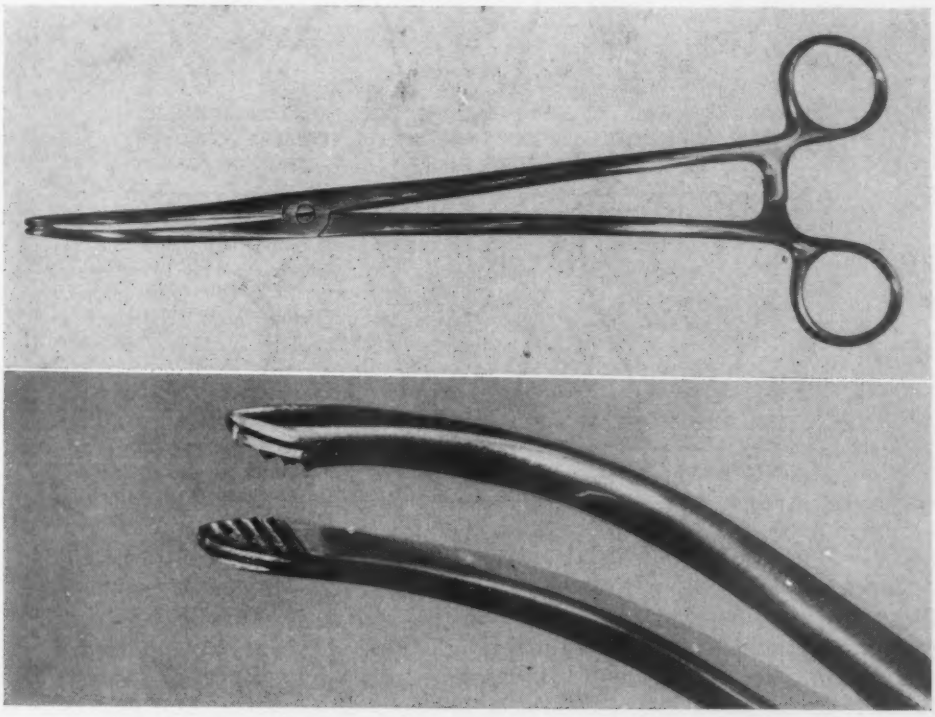


Fig. 1.—Amniotomy forceps.

"Response of Human Pregnant Uterus to Pitocin Tannate in Oil" he stated that "the most physiologic responses in severe primary uterine inertia have actually been obtained by giving an intravenous infusion of normal saline containing either 10 or 20 units of Pitocin to the liter. By constant observation and controlling the number of drops per minute, the obstetrician may control the character and amplitude of contractions quite adequately. The latter technique deserves further trial in selected cases of marked uterine inertia." Until Theobald and his collaborators[22] introduced the method by which the amount of oxytocin was restricted to physiological levels, induction of labor with pituitary extract was dangerous and sometimes lethal to both mother and fetus. Theobald[23] has further recorded his experience in 222 patients in whom

the Pitocin drip was used to induce labor; all but 20 of these were delivered vaginally. He believes that the onset of labor is related to a greatly increased sensitivity of the myometrium to oxytocin. He maintains that the drip must be given "in physiological amounts." The drip is started in a concentration of 1 unit or 2 units per liter and is never allowed to exceed 4 units per liter since the sensitivity of the uterine muscle may increase while the drip is being used. He asserts that if these strict precautions are taken, the routine use of the pitocin drip is safe in all patients who are allowed to go into labor. He has used the drip freely in the above concentrations in cases of contracted pelvis when the head is not engaged, in cases of placenta previa, accidental hemorrhage, triplets, in multiparas who have given birth to 13 or more children, and in patients who have previously been delivered by cesarean section.

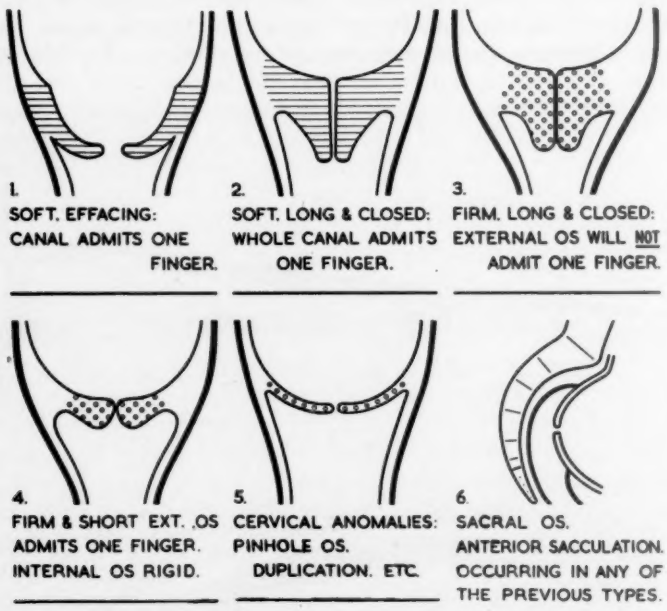


Fig. 2.—Types of cervix uteri at time of induction of labor.

Synthetic oxytocin: After the synthesis of oxytocin by du Vigneaud[5, 6] and others it has been possible for Boissonnas and his collaborators[3] to produce synthetic oxytocin by a different method. This substance Syntocinon,* is now available for therapeutic use. It has been shown by Bainbridge[1] and others that there is no qualitative difference between the natural and synthetic oxytocin. Mayes and Shearman[9] have also used Syntocinon to induce labor and found that it was just as effective as the natural product.

There is every reason to use this new product for it is a pure substance, free from vasopressor element. Its synthesis has been a major triumph for the biochemists.

Management of oxytocin infusion: The infusion consists of 5 units of oxytocin in 1 L. of 5 per cent dextrose, and is given at an initial rate of 5 to 10 drops per minute, preferably with tokograph recording of uterine contractions and tone and constant observation of the fetal heart rhythm. The infusion rate should be adjusted gradually until the contractions occur about every 2½ to 4 minutes without increase in the resting tone. This rate, which

*Sandoz Pharmaceuticals, Hanover, N. J.

should never exceed 40 drops per minute, is then maintained and the uterine action checked at intervals by the tokograph. If a sedative is given, its effect on the contractions is observed on the tokograph and the drip rate altered if necessary. When the effects of sedation begin to wear off the infusion rate may have to be reduced further, and the tokograph used again to check tone.

Sometimes infusion rates increase unexpectedly because of slipping of the clamp or changes in condition of the vein. Nylon catheters help to guard against this by limiting the maximum possible flow. Nevertheless, patients must be attended continuously and the fetal heart rate noted every 15 minutes. A graphic record should be made of the fetal heart rate, the infusion rate, and the time between contractions at quarter-hour intervals; maternal blood pressure should be noted hourly and, if raised above normal, then readings every quarter hour are necessary.

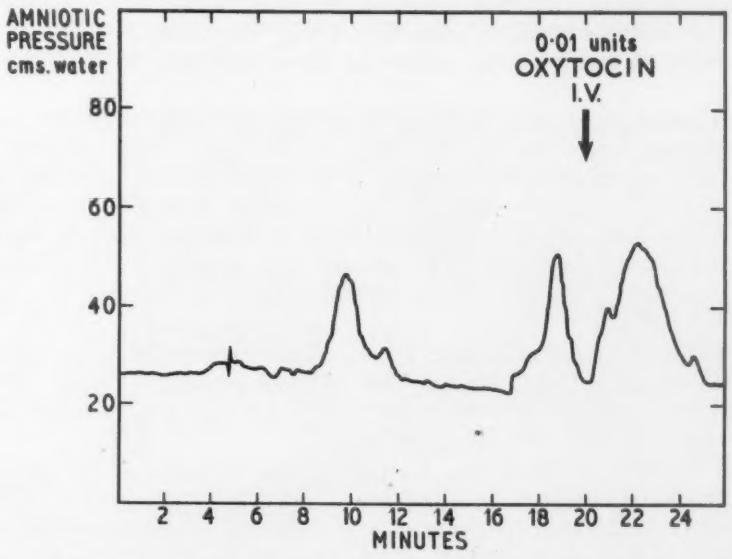


Fig. 3.—Oxytocin sensitivity test. Uterus responds to 0.01 unit of oxytocin intravenously.

If at any time it is felt that labor is established and that the oxytocin infusion is no longer required, the infusion should be changed to glucose only or slowed to less than 5 drops a minute for half an hour to test this assumption; then if normal and active contractions continue the infusion may be discontinued.

Condition of the Cervix Uteri at the Time of Induction

There are some obstetricians who attach no importance to the "maturity" of the cervix at the time of induction and who proceed with amniotomy whatever the state of the cervix. Cocks[4] at University College Obstetric Hospital has recorded in 133 cases the condition of the cervix at the time of surgical induction.

Fig. 2 depicts the types. Types 1 and 2 are the commonest, and 3 and 4 the least common. As one passes from Type 1 to Type 5 there is increasing difficulty in inserting the examining finger through the cervical canal. The "sacral os" is one which may cause difficulty and this kind of cervix will first have to be hooked down by the examining finger to below the presenting part to bring the cervical canal into its normal axis. Cocks found that in the "unripe" types (3 and 4) of cervix there was a longer induction-delivery interval and a

statistically greater number of operative deliveries than in Types 1 and 2. The "sacral os" was associated with a higher incidence of cesarean section and even in the presence of a Type 1 cervix there was a longer latent interval before the onset of labor if the os was sacral in position.

We believe that the cervix that is tough and sacral is unfavorable for induction and should be treated with respect. In such cases, provided immediate delivery is not urgent, it is more prudent to try to "mature" the cervix by intravenous oxytocin infusions and to delay rupture of the membranes until the cervix is more favorable and the uterus more sensitive.

Oxytocin Sensitivity (O.S.T.)

The oxytocin sensitivity test designed by Smyth,[15, 16, 18, 19] hereafter referred to as O.S.T., is a diagnostic test. In a series of cases it has shown a significant correlation with the time interval between induction and the onset of labor. The probability of this relationship being significant has been 200 to 1. The test provides no guide to the course of labor but only to its time of onset.

Amniotomy acts as an irritant because it allows an increase in the pressure of the presenting part upon the cervix, and where much fluid escapes, as in cases of hydramnios, provides a shortening of the myometrium to a more active length. Amniotomy by slightly traumatizing the cervix may also release chemicals (histamine) which act on the myometrium or nerves and help to stimulate contractility. Amniotomy, however, is a variable and usually weak irritant and is unlikely to be successful unless uterine irritability is very near to the level required for labor to begin.

Spontaneous uterine contractions do not occur unless the myometrium is biologically irritable. Sufficient irritability can be produced by intravenous oxytocin and the dose required is a measure of the degree by which the level of irritability falls short of that required for labor.

The oxytocin method of measuring irritability seems to be a useful guide to the obstetrician as to the choice of method for induction of labor in a particular patient. It has been found that patients on the verge of labor respond strongly, but safely, to doses of 0.01 unit oxytocin (Fig. 3), while other patients will require doses up to 0.1 unit. The measurement is therefore made between these limits. Early experience led to the decision to make the test by giving to each patient 0.01 unit each minute until an extra contraction was elicited and regarding the total dose as a measure of the sensitivity.

Studies have shown that it is advisable to consider patients sensitive to 0.04 unit oxytocin or less, as suitable for surgical induction; that is, they are very likely to go into labor within 24 hours after the induction. Those who require more than 0.04 unit to produce a uterine contraction should be treated first with an oxytocin infusion, and the amniotomy postponed until the uterus has become more sensitive.

The response of the uterus is measured by means of the Smyth guard-ring tokograph.[16]

This guage (Fig. 4), when applied to the abdomen over a fluid-filled part of the uterus, gives a true recording of the intra-amniotic pressure. Full details are given in the publication cited.

The Hazards of Induction of Labor

Recent British publications by Gibson,[8] Evans,[7] and Tennent and Black[21] have indicated the risks of induction. More recently, Parker[12] has reviewed 1,099 cases (19.8 per cent of all deliveries) in which labor was induced at the

Birmingham Maternity Hospital. There were 4 maternal deaths in the induction series with the introduction of infection at surgical induction a possible factor in 2 cases. The risk of sepsis to the mother and baby increases when operative delivery follows induction. Our practice is to start antibiotic treatment (500,000 units of penicillin and 0.5 Gm. of streptomycin every 12 hours) when the membranes have been ruptured for 24 hours. Since the introduction of this routine, uterine sepsis has never been a serious complication.

Fetal hazards are due to prolapse of the cord, separation of the placenta, and damage to the fetal vessels in the placenta. With care and by using only low amniotomy, these risks can be diminished.

The failure of labor to become established 24 hours after amniotomy causes anxiety to both patient and obstetrician. Another 24 hours may be allowed to elapse provided oxytocin infusion is started. If, after this time (48 hours), there has not been progressive dilatation of the cervix, cesarean section must be considered. This may prove safer for both mother and baby than delay in the hope of a vaginal delivery.

Fig. 4.—Smyth guard-ring tokograph and recording apparatus.

Induction of Very Premature Labor for Living or Dead Fetus

Induction of labor between 28 and 36 weeks presents much greater difficulty than it does at term. Some consideration of the differences in this problem makes the differences in treatment rational.

First, the uterus is not fully grown or filled and there is normally a thick muscular wall in the part of the uterus above the cervical canal and below the bulk of the conceptus. Before pressure can be brought to bear upon the canal at the level of the internal os at least one of three things must take place: (1) the uterus must be further distended with fluid or by fetal growth, (2) there must be relative retraction of fundal muscle, or (3) the membranes must be ruptured so that the presenting part can descend through the lower segment to reach the os.

The methods available to achieve these ends are growth or artificially induced hydramnios (this has never to our knowledge been tried but is nevertheless a rational method for distending the lower segment), tone-increasing doses

of oxytocic drugs, especially ergometrine, and rupture of the forewaters. Oxytocin infusions gradually tend to produce a more favorable distribution of muscle away from the lower pole but the process is a slow and lengthy one and is practicable only when about a week is available for the treatment. It is said that oral quinine therapy and estrogen therapy to toleration limits accelerate the process and this may be so but the required changes can be brought about only very slowly. They ought to be added to the process when practicable as they certainly do not decelerate it; many authorities advise them. When the fetus is dead all these methods are suitable, although the dangerous possibilities of amniotic fluid emboli have been reported when tonic contractions are produced after amniotomy. Rupture of the membranes or intrauterine procedures carry a danger of anaerobic infection of dead tissues and if these procedures are risked there must be prophylatic antibiotic irrigation. Delivery of a dead fetus is often more rapidly accomplished than of a living one since in any event there is a natural tendency toward abortion and the dead conceptus may more readily descend to the cervix.

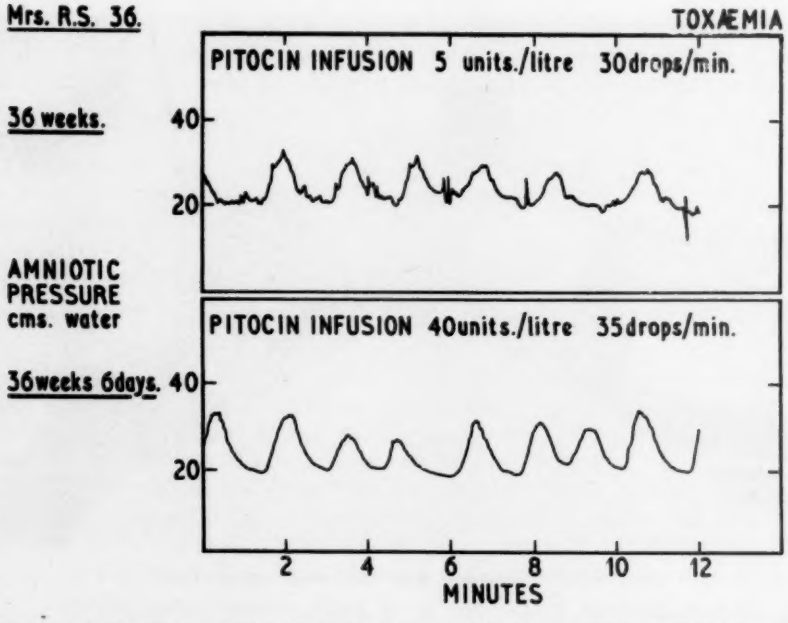


Fig. 5.—Continuous Pitocin infusion for 1 week at 36 weeks' gestation. Sensitivity of uterus not increased even with infusion of 40 units per liter.

With a living fetus amniotomy with antibiotic cover is safer, but the use of quinine, which causes fetal distress, is contraindicated, and of course oxytocic treatment must not be severe enough to produce fetal distress, which in effect limits the treatment to weak oxytocin infusions.

With these treatments, as well with all other use of oxytocic drugs, the healthiness and parity of the uterus must be considered before the induction of tonic contractions in excess of those likely to be encountered in ordinary labor.

With a *dead* fetus, priming of the uterus with large doses of estrogen and quinine may increase its sensitivity to oxytocin infusion. The latter should consist of 10 units to a liter of 5 per cent dextrose. The use of a nylon catheter into the vein will allow continuous infusion over a long period. The infusion, with occasional tokograph control, should run daily until painful contractions are obtained and there are changes in the cervix characteristic of the onset of

labor. At this stage, the infusion should be kept going at night too, supplemented at hourly intervals by a massive dose of oxytocin to give a long-lasting contraction (½ unit into the transfusion tubing).

Fig. 5 is a record of continuous Pitocin infusion given for one week for fetal death at the thirty-sixth week of pregnancy. The uterus became gradually less sensitive to Pitocin and even an infusion of 40 units per liter did not increase its sensitivity. With this treatment, however, the cervix became mature and spontaneous delivery followed.

Treatment with oxytocin can be carried out entirely by recurrent intramuscular (1 unit) or intravenous (0.25 unit) injection but an unduly large number of injections is required. The tonic contractions thus induced are more uncomfortable and tiring to the patient than those associated with a regular rhythm.

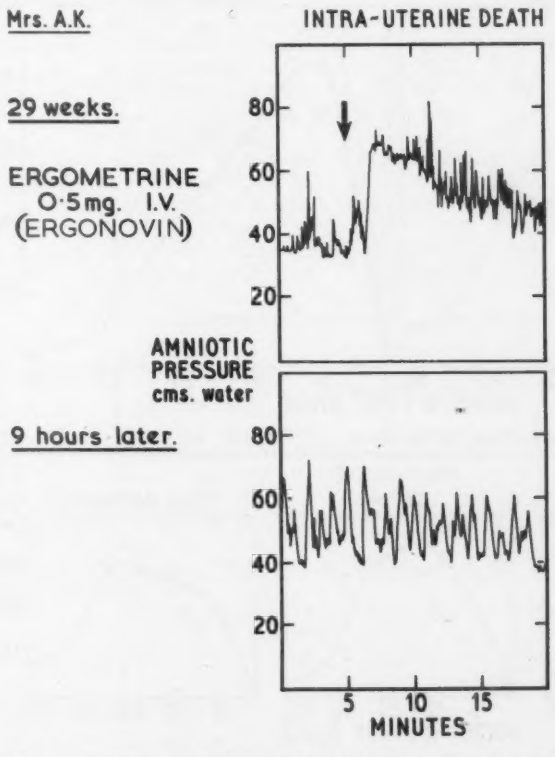


Fig. 6.—Spasm of uterus induced with intravenous ergometrine (ergonovine).

Fig. 6 shows the spasm of the uterus induced by an intravenous injection of ergonovine with subsequent establishment of regular contractions. The fetus was dead at 29 weeks' gestation, and a drip infusion of this drug was later used and spontaneous delivery followed after 3 days of this treatment.

Statistical Correlation of Clinical Data at University College Hospital

It has been possible by means of a punch card system to collect data concerning 3,750 deliveries (1953-1955) and to correlate factors in relation to induction. During this period the induction rate was 15.2 per cent and the average length of labor (first stage) was reduced by 5.8 hours for primigravidas and by about 2.2 hours for multiparas by amniotomy. There was no difference in the forceps, postpartum hemorrhage, occipitoposterior presentation, fetal

distress, and stillbirth rates. The average weight of the babies was not different from that of those born after spontaneous labor. In all patients the incidence of induction increased with age.

It will be seen from Fig. 7 that the duration of labor depends on the time at which the membranes rupture and the associated maternal condition. When they rupture before labor, whether spontaneously or artificially, labor is shorter.

Amniotomy shortens labor no matter what the indication. For instance, labors with toxemia and amniotomy are shorter than with toxemia alone, and with postmaturity and amniotomy are shorter than with postmaturity alone.

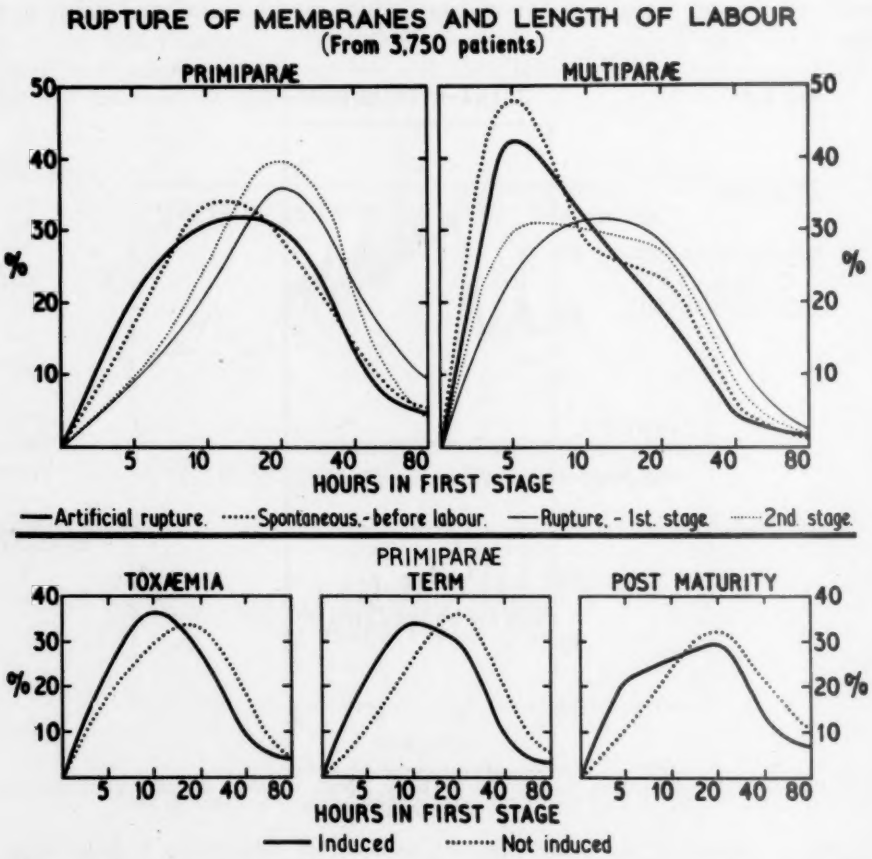


Fig. 7.—Duration of labor in relation to rupture of the membranes and condition of the mother.

Comparison of the length of the first stage of labor reveals a reduction in the average time both for patients who have had amniotomy and for those whose membranes rupture spontaneously just before the onset of labor. There is no significant difference between the two groups but in both the first stage is shorter than that for patients whose membranes rupture during the first or second stage of labor.

Conclusion

Low amniotomy is the modern, rational, and safe procedure for the induction of labor provided there is a proper indication and selection of cases. The

presence of intact membranes is of no advantage to labor and there should be no hesitation in doing this operation except in patients with a dead fetus or a fetus of less than 34 weeks' gestation. Other methods should be discarded except for the use of oxytocin infusion when amniotomy is contraindicated or in addition to amniotomy when the uterus is not sufficiently irritable. The irritability of the uterus and the state of the cervix are the factors that will decide whether oxytocic treatment is necessary.

References

1. Bainbridge, M. N., Nixon, W. C. W., Schild, H. O., and Smyth, C. N.: Brit. M. J. 1: 1135, 1956.
2. Bell, W. Blair: Brit. M. J. 2: 1609, 1909.
3. Boissonnas, R. A., Guttman, S., Jaquenand, P. A., and Waller, J. P.: Helvet. chim. acta 38: 1491, 1955.
4. Cocks, D. P.: Brit. M. J. 1: 327, 1955.
5. du Vigneaud, V., Ressler, C., Swan, J. M., Roberts, C. W., Katsoyannis, P. G., and Gordon, S.: J. Am. Chem. Soc. 73: 4879, 1953.
6. du Vigneaud, V., Ressler, C., Swan, J. M., Roberts, C. W., Katsoyannis, P. G., and Gordon, S.: J. Am. Chem. Soc. 76: 3115, 1954.
7. Evans, G.: Lancet 2: 564, 1954.
8. Gibson, G. B.: J. Obst. & Gynaec. Brit. Emp. 59: 814, 1952.
9. Mayes, B. T., and Shearman, R. P.: J. Obst. & Gynaec. Brit. Emp. 63: 812, 1956.
10. Moir, J. Chassar: Munro Kerr's Operative Obstetrics, ed. 6, London, 1956, Baillière, Tindall & Cox, p. 626.
11. Page, E. W.: Proc. Soc. Exper. Biol. & Med. 52: 195, 1943.
12. Parker, R. B.: J. Obst. & Gynaec. Brit. Emp. 54: 94, 1957.
13. Russell, J. K., Smith, D. F., and Yule, R.: Brit. M. J. 2: 1414, 1956.
14. Smyth, C. N.: Proc. Internat. Congress on Obst. & Gynec., Basle, 1954, Sandoz S. A., p. 79.
15. Smyth, C. N.: Proc. Roy. Soc. Med. 48: 677, 1955.
16. Smyth, C. N.: J. Obst. & Gynaec. Brit. Emp. 64: 59, 1957.
17. Smyth, C. N.: Lancet 2: 987, 1957.
18. Smyth, C. N.: Lancet 1: 237, 1958.
19. Smyth, C. N.: Triangle 3: 150, 1958.
20. Smythe, H. J. Drew: Brit. M. J. 1: 1018, 1951.
21. Tennent, R. A., and Black, M. D.: Brit. M. J. 2: 833, 1954.
22. Theobald, G. W., Graham, A., Campbell, J., Gange, P. D., and Driscoll, W. J.: Brit. M. J. 2: 123, 1948.
23. Theobald, G. W., Kelsey, H. A., and Muirhead, J. M. B.: J. Obst. & Gynaec. Brit. Emp. 63: 641, 1956.
24. Walker, J.: J. Obst. & Gynaec. Brit. Emp. 61: 162, 1954.

THE USE OF CHLORPROMAZINE IN OBSTETRICAL ANALGESIA*

CHARLES IVERSON BRYANS, JR., M.D., AND
CHARLES MCL. MULHERIN, M.D., AUGUSTA, GA.

(From St. Joseph's Hospital)

IN AUGUSTA, Georgia, for the past 10 years or more, practically all the obstetricians have used intravenous barbiturates for obstetrical analgesia as described by Volpitto in 1946.[1] The technique, in brief, is as follows: 250 mg. of pentobarbital sodium (Nembutal) and 0.6 mg. scopolamine are mixed and diluted to 10 c.c. with sterile water. This solution is administered slowly as needed. It has been the custom to keep the patient sedated to the extent that she sleeps throughout labor, although she may be restless during contractions. Complete amnesia is obtained in nearly 100 per cent of cases. No additional anesthesia is needed for spontaneous delivery. Usually the patient is given cyclopropane for episiotomy repair and also for any operative procedure necessary, although some obstetricians including one of us (C. I. B.) prefer pudendal block.

This method has been a fairly satisfactory one but we were dissatisfied with the rather high incidence of maniacal excitement and the comparatively large number of depressed babies. Therefore, when the early reports on the use of chlorpromazine (Thorazine) came out in this country, we decided that this drug was worthy of a trial.

Material and Method

Chlorpromazine hydrochloride is an amine derivative of phenothiazine. Martin and co-workers[2] stated that it is a selective central depressant which acts on the sensory, motor, and autonomic levels of the thalamus, the basal ganglia, and the hypothalamus. There is a peripheral diminution of activity of the pituitary, adrenal, and thyroid glands. It exerts a protective action against traumatic and hemorrhagic shock. It was first synthesized in 1950 by Charpentier in France, where it is known as Largactil. It was soon in wide use in Europe, particularly in hibernation anesthesia.[3, 4] In this country it was first used as an antiemetic drug[5] and later as a sedative or tranquilizer[6-9] and as a potentiator of sedative and analgesic agents.[2] In August, 1954, Hershenson and associates[10] published their preliminary report on the use of the drug in labor. Since the beginning of our study, there have been a number of published reports on its use in obstetrical analgesia.[11-18]

We began to use chlorpromazine on Nov. 23, 1954. We used it tentatively at first, trying different doses and combinations with barbiturates, meperidine,

*Presented at a meeting of the Georgia and South Carolina Obstetrical and Gynecological Societies, Columbia, S. C., Nov. 3, 1957.

and scopolamine. After several months of trial we were using it routinely in the following manner: When the patient was in well-established labor and began to complain of discomfort she was given 25 mg. of chlorpromazine, 50 mg. of meperidine, and 0.6 mg. of scopolamine all mixed in the same syringe and injected in the gluteal muscle. The medication was repeated in doses of half this amount as needed throughout labor. The second dose was usually given in about one hour and subsequent doses at intervals of 2 to 3 hours. After the establishment of the routine, the only patients who were not handled in this way were those whose labors were progressing so rapidly that it was felt that intramuscular medication would not be effective. We were afraid to give chlorpromazine intravenously in view of the reports of frequent hypotensive reactions. Patients in premature labor were given chlorpromazine and scopolamine without the meperidine.

From Nov. 23, 1954, through Dec. 31, 1956, 628 patients received chlorpromazine in total dosage ranging from 25 to 150 mg. The mean total dose of the three drugs was chlorpromazine, 50 mg., meperidine, 100 mg., and scopolamine, 1.2 mg. These were all private patients of the authors, who were practicing together at that time. They were all white women and were treated at the same hospital, St. Joseph's.

For comparison we have data on 581 patients delivered by the same two obstetricians in the same hospital in the year preceding this study, or from Nov. 23, 1953, through Nov. 22, 1954. These will hereafter be referred to as Groups I and II, respectively.

That these series are comparable can be shown by the following: The average ages of the two groups were 26.1 and 26.0 years. The average parity of the parous patients was 1.8, and 1.9 children. The number of primigravidas in Group I (chlorpromazine) was 195, or 31.0 per cent, and in Group II (patients delivered in the year prior to the study) was 160, or 27.5 per cent.

Duration of Labor and Method of Delivery

It has been thought by some that chlorpromazine might retard labor. In our series we find the average duration of labor to be 9 hours and 22.8 minutes, and 8 hours and 12.5 minutes in Groups I and II, respectively (Table I). It must be remembered that Group I excludes all patients whose labors were progressing very rapidly. If these patients (who did not get chlorpromazine) are included, we find the average duration of labor to be 8 hours and 33.5 minutes. It therefore appears that chlorpromazine had no significant effect on the length of labor in this series.

TABLE I. A COMPARISON OF RESULTS IN CHLORPROMAZINE-TREATED AND NONTREATED GROUPS

	GROUP I 628 PATIENTS	GROUP II 581 PATIENTS	CHI-SQUARE VALUE
Average duration of labor	563 minutes	493 minutes	6.29*
Spontaneous delivery (vertex)	68.6%	70.7%	.636
Breech deliveries	3.0%	3.4%	.466
Forceps	26.8%	23.8%	1.21
Cesarean sections	1.6%	2.1%	.478
Depressed infants	3.3%	7.6%	2.66
Stillbirths	3.0%	0.8%	7.26*
Neonatal deaths	1.8%	1.4%	.272

*Chi-squared values greater than 3.84 indicate that there is a statistical difference at the .05 level between the groups being tested.

It has been said that the action of chlorpromazine simulates in some ways that of a spinal anesthetic. If this be true, we would expect to find an increased number of operative deliveries. It should be said parenthetically at

this point that we did not use routine outlet or prophylactic forceps but did not hesitate to apply forceps whenever they were felt to be necessary for fetal distress, persistent occiput posterior, transverse arrest, or simply delayed second stage.

In Group I (chlorpromazine) there were 431 spontaneous cephalic deliveries, or 68.6 per cent, and in Group II, 410, or 70.6 per cent. Again we come to the conclusion that the use of the drug has had no effect on the outcome in this respect.

When we analyze the forceps deliveries, however, we find a difference. In Group I there were 168 forceps deliveries, or 26.8 per cent, and in Group II, 132, or 22.7 per cent. This fits in with the foregoing figures. But when we separate the low-forceps deliveries from the midforceps we find the percentage of midforceps deliveries to be 11.0 per cent, and 4.6 per cent, respectively. This would lead us to believe that, as with spinal and caudal anesthesia, there is a relatively high incidence of persistent occiput posterior and deep transverse arrest due probably primarily to the fact that the patient is less inclined to "bear down" during the second stage.

There were 10 cesarean sections, or 1.6 per cent, in Group I as compared to 12 (2.1 per cent) in Group II. The indications for section in Group I were fetopelvic disproportion in 4 cases, abruptio placentae in 2, placenta previa in 2, and one case each of prolapse of the cord and brow presentation. In Group II, 6 sections were elective repeat operations. Of the remaining 6 (1.03 per cent), 3 were done for abruptio placentae and one each for brow presentation and fetopelvic disproportion. One section was done on a patient who developed tetanic uterine contractions soon after an intravenous Pitocin infusion was begun in treatment of uterine inertia.

Fetal and Neonatal Mortality

The greatest danger involved in most of our current techniques of obstetrical analgesia which involve the use of narcotic or hypnotic drugs is respiratory depression of the newborn. When we compare the data on the infants in our series we find that, in Group I, 21, or 3.3 per cent, and in Group II, 44, or 7.6 per cent, of the infants were significantly depressed. It has been the custom in Augusta, whenever an infant did not breathe spontaneously or respond to gentle stimulation, immediately to insert a tracheal catheter and give artificial respiration by means of a Torpin insufflator.[19] This was done in each of these cases. Group II consists of all deliveries in the year prior to this study. We find that the incidence of depressed babies was more than twice that of the chlorpromazine group: 7.6 per cent as compared to 3.3 per cent. If we break the chlorpromazine group down into those who received only the routine medication and those who received varying doses of barbiturates as well, we find the percentage of depressed babies to be only 2.8 per cent, or just a little over one third that of Group II. Whether the improvement in the condition of the newborn is due to the paradoxical effect on respiration of chlorpromazine when used with meperidine as described by Reckless,[20] or to the potentiating action which enables us to use smaller doses of meperidine, we cannot say.

Of the depressed babies in the chlorpromazine group, all but 2 were discharged in good condition.

There were 9 stillborn infants (1.4 per cent) in Group I and 5 (0.8 per cent) in Group II. Of the 14 stillborn infants all but 3 were dead (no fetal heart tones heard) on admission to the hospital. In only one of these 3 cases was chlorpromazine administered. This was a pregnancy of 6½ months' duration with a face presentation. There was a partial abruptio placentae and the fetal heart tones disappeared during labor.

Eleven (1.8 per cent) neonatal deaths occurred in Group I and there were 8 (1.4 per cent) in Group II. Of the 11 infants that died neonatally in the chlorpromazine group, 6 were premature, the largest weighing 1,500 grams. There were 2 severe cases of erythroblastosis, and one case of circumvallate placenta with partial abruptio placentae. This infant was delivered by cesarean section and was in very poor condition at birth. It never breathed spontaneously. Of the others, there was one case of prolonged labor terminated by midforceps and one assisted breech delivery. The first of these latter infants died after one hour of intratracheal insufflation. The second was not obviously depressed and was not insufflated. It died after about 6 hours of unknown cause. It is doubtful that the Thorazine could have had any effect one way or the other on this group.

Toxicity

The most common and most feared side effect of the drug is a sudden precipitate drop in blood pressure. Harer[16] concluded, "It produces unpredictable and marked hypotension in about 18 per cent of patients in labor" and "the potential hypotensive effects of chlorpromazine in labor must be considered dangerous to both mother and fetus." We did not find this to be so in our patients. There was only one episode of severe hypotension in this series of 628 patients, an incidence of 0.16 per cent.

In addition to the cases studied there have been at least 1,800 women, patients of other doctors, delivered at the same hospital during the time of this study, who received chlorpromazine. No alarming drops in blood pressure were noted in any of these patients.

As far as any other episodes of hypotension, of any degree, are concerned, we could find no correlation between the blood pressure and the administration of the drug. The blood pressure of a pregnant woman is notoriously labile. There were frequent drops in blood pressure of 10 or even 20 ml. There were also unexplained elevations. This seemed to be equally true in patients who did and in those who did not receive chlorpromazine.

The patient who did show severe hypotension was a 37-year-old gravida iv, para ii, in early labor. She was given the routine injection of chlorpromazine, 25 mg., meperidine, 50 mg., and scopolamine, 0.6 mg. Shortly thereafter her blood pressure dropped to 65 mm. systolic. The diastolic pressure was unobtainable. The patient was alert and had no complaints except that she also had a severe urticarial reaction. An intravenous infusion of 1,000 c.c. of 5 per cent glucose in water with 4 c.c. of 0.2 per cent levarterenol bitartrate (Levophed) was started immediately and the blood pressure soon returned to normal. The urticaria soon subsided and about 2 hours later she was spontaneously delivered of a normal 3,330 gram female infant.

The other principal toxic (or allergic) manifestation of chlorpromazine is jaundice of the obstructive type. This is said to occur mainly, however, in patients who have received the drug over a long period of time.[16] There was no jaundice noted in any of the 628 patients in this series, nor was there any in the approximately 1,800 other patients who also received the drug during this period.

There was no instance of blood dyscrasia and no other complications were noted.

Comment

The greatest advantage in the use of chlorpromazine over the method previously used is so subjective that we have attempted no statistical analysis or

comparison. There is no doubt, however, in the minds of the authors, the labor and delivery room nurses, and the other obstetricians who have observed these patients that they were very much quieter and more controllable than those given sedation with barbiturates and scopolamine. All patients queried were more than pleased with the method. Most of the other obstetricians have adopted our routine.

As a matter of general interest and to round out our statistics, it should be recorded that the incidence of breech deliveries in the two series was 3.0 per cent and 3.4 per cent. This is about the expected incidence. There were 2 face presentations. The incidence of twins was 0.5 per cent and 0.9 per cent, which is surprisingly low.

Summary

1. We have studied 628 obstetrical deliveries in which chlorpromazine was used as part of the medication to produce analgesia and amnesia. The dose varied from 25 to 150 mg. The average patient received, in all, chlorpromazine, 50 mg., meperidine, 100 mg., and scopolamine, 1.2 mg.

2. Chlorpromazine had no effect on the duration of labor.

3. It did not increase the total number of operative deliveries but may have increased the incidence of midforceps.

4. The incidence of respiratory depression in the infants of the chlorpromazine patients was less than one half that found among the babies delivered in the year prior to the use of this drug.

5. There was only one episode of hypotension in the whole series. There was no incidence of jaundice. Also, there were no significant hypotension and no jaundice in approximately 1,800 other women, patients of other doctors, who were delivered in the same hospital during the course of this study.

6. The patients were quiet and cooperative, and the incidence of amnesia was nearly 100 per cent.

Conclusion

We feel that in chlorpromazine we have a drug that is safe for the mother and baby and one that enables us to produce a high degree of analgesia and amnesia without psychomotor excitement.

References

1. Volpitto, P. P.: J. A. M. A. 132: 1059, 1946.
2. Martin, E. M., Koeppe, R., Smith, D. A., and Grant, G.: Bull. Acad. Med., Toronto 27: 175, 1954.
3. Dundee, J. W.: Brit. J. Anaesth. 26: 357, 1954.
4. Hopkin, D. A. B.: Lancet 1: 605, 1955.
5. Friend, D. G., and Cummins, J. F.: J. A. M. A. 153: 480, 1953.
6. Lehmann, H. W., and Hanrahan, G. E.: A. M. A. Arch. Neurol. & Psychiat. 71: 227, 1954.
7. Winkelman, N. W., Jr.: J. A. M. A. 155: 181, 1954.
8. Albert, S. N., Rea, E. L., Duverney, C. A., Shea, J., and Frazekas, J. F.: M. Ann. District of Columbia 232: 245, 1954.
9. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W.: J. A. M. A. 155: 626, 1934.
10. Hershenson, B. B., Isaak, S. J., Romney, S. L., and Reid, D. E.: New England J. Med. 251: 216, 1954.
11. Davis, J. I.: Canad. Anaesth. Soc. J. 2: 327, 1955.

12. Carroll, J. J., and Hudson, P. W.: Canad. Anaesth. Soc. J. 2: 340, 1955.
13. Karp, M., Lamb, V. E., and Benaron, H. B. W.: AM. J. OBST. & GYNEC. 69: 780, 1955.
14. Anz, W. E., and Smith, L. J.: AM. J. OBST. & GYNEC. 71: 1242, 1956.
15. Shaffer, A. L.: Obst. & Gynec. 8: 1, 1956.
16. Harer, W. B.: Obst. & Gynec. 8: 1, 1956.
17. Quinquilla, R. L.: J. Arkansas M. Soc. 53: 97, 1957.
18. Norton, H. I., Weingarten, M., and McDonough, E. T.: AM. J. OBST. & GYNEC. 71: 1251, 1956.
19. Volpitto, P. P., and Torpin, R.: South. M. J. 35: 559, 1942.
20. Reckless, D.: Anesthesia 9: 288, 1954.
21. Doughty, R.: Science Information Department, Smith Kline & French Laboratories, Philadelphia, August, 1955.

INTRAMUSCULAR PERPHENAZINE* IN LABOR

A Study of 700 Patients

T. G. Gready, Jr., M.D., William J. Estrada, M.D., and Joe Haden, M.D., Houston, Texas

(From the Department of Obstetrics and Gynecology, Hermann Hospital, and the Baylor University College of Medicine, Texas Medical Center)

MANY tranquilizers are currently being used to potentiate the effect of analgesic drugs during labor. Some of them have been associated with undesirable side reactions such as hypotension, jaundice, etc. In this investigation we have attempted to evaluate perphenazine, a new amino derivative of chlorphenothiazine, for its effectiveness in (1) reducing the amount of narcotic required for satisfactory analgesia and anesthesia, (2) reducing fetal narcosis, and (3) producing the desired tranquilizing and antiemetic response.

Perphenazine is generally similar to its older analogue, chlorpromazine, but laboratory studies[1-5] have shown perphenazine to possess 5 to 10 times the behavioral potency and two thirds the toxicity of the latter drug. The adrenergic blockade appears to be much lower with perphenazine than with other agents in its class and this probably accounts for the decreased incidence of hypotension. Perphenazine also has marked antiemetic properties.[6-9] Its clinical indications include premedication for surgical anesthesia where it usually decreases the amount of narcotic required.

Harer[10] compared injections of chlorpromazine and perphenazine among 50 patients in labor. Both drugs decreased apprehension and emesis but 5 times as much chlorpromazine was required to duplicate the effect of 10 mg. perphenazine. He also used perphenazine orally at the beginning of labor in 200 patients, providing identical placebos to another 200 patients as a control. The salutary effects of perphenazine were marked and there were no adverse effects on mother or child.

Method

This study was undertaken at the Hermann Hospital consecutively during the year between March, 1957, and March, 1958, except for a few months when the series was unavoidably delayed. There are approximately 6,000 deliveries a year at this hospital, of which approximately 1,750 are on the clinic service.

Perphenazine was administered to a total of 1,200 obstetric patients of whom 700 are reported. (Excluded from this series are the patients who

*Supplied as Trilafon through the courtesy of J. Black, M.D., Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

were given injections less than 1 hour before delivery or who received less than 5 mg. perphenazine during the early part of the study when we were determining optimal dosage levels. Also excluded were certain patients in premature labor who did not receive medication.) The group of 700 patients (228 primiparas and 472 multiparas) came from the private and clinic services, with the majority from the clinic. The 300 patients (104 primiparas and 196 multiparas) who served as controls were all from the private service.

The dose of perphenazine given to 176 patients was 5 mg., to 491 patients 10 mg., and to 33 patients 15 to 25 mg. Originally 5 mg. or less was used in all cases, but later the usual dose was changed to 10 mg. since the latter was found necessary for the full narcotic-potentiating effect. Meperidine (Demerol) was administered to all patients in this group. The usual dose, for 667 patients, was 50 mg. but some received 100 mg. All patients received scopolamine, $\frac{1}{200}$ to $\frac{1}{100}$ grain. Patients who were admitted early in labor received pentobarbital (Nembutal), $1\frac{1}{2}$ to 3 grains orally. Barbiturates were administered to 128 patients, of whom 38 were in the group who received 5 mg. perphenazine and 90 were in the group who received 10 mg. or more. The injectables were mixed in the same syringe and given intramuscularly. When necessary, repeat injections of the same amount or less were given. Two injections were required in 85 patients and three injections in 5.

Hypotensive agents such as veratrum viride (Veriloid), hydralazine (Apresoline), and reserpine (Serpasil) were administered alone or in combination to 40 patients in the perphenazine group. Oxytocin (Pitocin) was used in 48 patients for the induction of labor and in 9 patients for the stimulation of labor.

Complications of labor were present in 69 cases; these patients later received perphenazine. There were 5 patients with essential hypertension and 4 with cardiac disease. Pre-eclamptic toxemia was present in 49 and eclampsia in 2. Abruptio placentae was seen in 5 patients, placenta previa in 2, and ruptured marginal sinus in 2. The incidence of these complications was approximately the same as that to be found in an unselected obstetric population. Perphenazine was used in all cases, even if complications were present, and patients were observed closely for evidence of reaction or toxicity.

In the 300 control patients, the usual dosage of meperidine was 100 to 125 mg. (200 patients), although 68 received 50 or 75 mg. and 32 received 150 to 200 mg. Scopolamine, $\frac{1}{200}$ to $\frac{1}{100}$ grain, was also administered to all. Barbiturates were given to 56 of the 300 control patients and tranquilizers other than perphenazine to 47.

The types of anesthesia used in the perphenazine group and in the control group are summarized in Table I. Saddle-block anesthesia was employed most frequently. This anesthesia is used in this hospital for most clinic and many private obstetric patients.

TABLE I. TYPES OF ANESTHESIA

ANESTHESIA	PERPHENAZINE GROUP			CONTROL GROUP		
	PRIMIPARAS	MULTIPARAS	TOTAL	PRIMIPARAS	MULTIPARAS	TOTAL
Saddle block	211	395	606	76	112	188
Cyclopropane	12	19	31	27	64	91
Nitrous oxide	0	5	5	0	2	2
Ether	0	2	2	0	0	0
Pudendal	3	21	24	0	1	1
None	2	30	32	1	17	18
Total	228	472	700	104	196	300

TABLE II. RESULTS IN PERPHENAZINE-TREATED GROUP

DOSAGE (ALL WITH SCOPOLAMINE, 1/200 TO 1/100 GRAIN)	NO. OF PATIENTS	EVALUATION BY PHYSICIAN AND NURSE			EVALUATION BY PATIENT		
		GOOD	FAIR	POOR	GOOD	FAIR	POOR
Perphenazine, 5 mg., meperidine, 50 mg., + barbiturate	38	32	5	1	29	6	3
Perphenazine, 5 mg., meperidine, 50 mg.	138	119	5	14	110	9	19
Perphenazine, 10 mg., meperidine, 50 mg. + barbiturate	90	80	6	4	80	4	6
Perphenazine, 10 mg., meperidine, 50 mg.	401	357	17	27	346	22	33
Perphenazine, 15-25 mg., meperidine, 100 mg.	33	16	10	7	12	11	10
Total	700	604 (86.3%)	43 (6.1%)	53 (7.6%)	577 (82.4%)	52 (7.4%)	71 (10.2%)

TABLE III. RESULTS IN CONTROL GROUP

DOSAGE (ALL WITH SCOPOLAMINE, 1/200 TO 1/100 GRAIN)	NO. OF PATIENTS	EVALUATION BY PHYSICIAN AND NURSE			EVALUATION BY PATIENT		
		GOOD	FAIR	POOR	GOOD	FAIR	POOR
Meperidine, 50-75 mg., + barbiturate	13	6	5	2	6	4	3
Meperidine, 50-75 mg.	55	36	11	8	33	7	15
Meperidine, 100-125 mg., + barbiturate	36	29	4	3	26	4	6
Meperidine, 100-125 mg.	164	149	9	6	140	8	16
Meperidine, 150-200 mg., + barbiturate	7	6	1	0	7	0	0
Meperidine, 150-200 mg.	25	21	3	1	22	3	0
Total	300	247 (82.3%)	33 (11.0%)	20 (6.7%)	234 (78.0%)	26 (8.7%)	40 (13.3%)

It was of course not possible to make an exact or quantitative assessment of results. The evaluations were made according to observed response and subjective reports. "Good" results were recorded if the patient was quiet and asleep or nearly so between contractions, and had minimal discomfort during contractions. The "fair" and "poor" groups were then classified accordingly. Following delivery, patients were questioned about pain during labor and these statements were also classified.

Results

The evaluations by physicians and nurses of the patients who received perphenazine are shown in Table II. Good results were obtained in 604 patients (86.3 per cent). As would be expected, results were somewhat better among the multiparas. Evaluations by patients themselves differed little from the objective findings. Good results were reported by 82.4 per cent with, again, better reports from the multiparas. The optimal dose was 10 mg. perphenazine, 50 mg. meperidine, and $\frac{1}{200}$ to $\frac{1}{100}$ grain scopolamine.

The controls responded less favorably although the difference was not marked (Table III). "Good" results were reported by the medical staff among 247 patients (82.3 per cent). In the control group, according to evaluations by patients, good results occurred in 234 (78.0 per cent). Again, the multiparas had better objective and subjective results than did the primiparas.

These results indicate that patients in the perphenazine group did as well as or better than those in the control group on significantly lower doses of meperidine.

The effect of perphenazine on nausea and vomiting was dramatic. The emesis which occurs fairly frequently after injections of opiates and scopolamine was almost entirely absent among the perphenazine-treated group. Only 4 per cent of the patients in this group had nausea and/or vomiting, as compared to 14 per cent among the controls.

No side effects were encountered from perphenazine in any of the 700 patients in this series, and the total experience with this agent (1,200 obstetric patients) has been free from evidence of toxic reactions. Transient nuchal rigidity or extrapyramidal symptoms, which have been reported as side effects of perphenazine, did not occur in this series. Undoubtedly, the low doses used (rarely over 10 mg. and never over 25 mg.) accounted for the absence of sequelae, since side effects of perphenazine are reported to be related to the dosage level. Six patients, all primiparas, were uncooperative, disoriented, and hyperactive. Although this reaction has been reported occasionally following administration of the high-potency phenothiazines, it was not felt that perphenazine was responsible in this series. Meperidine and scopolamine also can cause this type of reaction. It occurred, in this series, equally in both the perphenazine-treated and control groups.

Perphenazine neither increased nor decreased the blood loss: there was no appreciable difference between the perphenazine-treated patients and those in the control group. There were 8 postpartum hemorrhages in the perphenazine group (1.1 per cent) and 4 (1.3 per cent) in the controls.

There was no drop in blood pressure which could be attributed to perphenazine. This finding is considered to be of particular significance in view of the fact that in a previous series with chlorpromazine and veratrum viride there were 3 cases of marked hypotension, 2 requiring therapy with levarterenol (Levophed), and in a previous series with promethazine one patient exhibited marked hypotension. Blood pressure depressions greater

than 20 mm./Hg were encountered in a few patients who received saddle-block anesthesia. A level of anesthesia higher than is desirable was undoubtedly responsible since these effects occurred equally in the perphenazine group (7 patients; 1.1 per cent) and in the control group (3 patients; 1.6 per cent) and did not occur with other types of anesthesia. Perphenazine was used safely with all types of obstetric anesthesia.

The types of delivery among patients who received perphenazine are summarized in Table IV. The drug did not affect the mechanics or type of delivery in any patient. Generally, patients who are scheduled for cesarean section are not admitted to the labor division and therefore only 3 such patients appear in our series.

TABLE IV. TYPES OF DELIVERY WITH PERPHENAZINE

TYPE OF	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	51	252	
Low forceps	147	171	
Forceps rotation	20	35	
Breech	8	13	
Cesarean section	2	1	
Episiotomy	222	243	
Total	228	472	700

Perphenazine did not speed, slow, or stop labor. The incidence of slowed and stopped labor in both groups was equal (Table V).

TABLE V. EFFECT ON LABOR

	PERPHENAZINE GROUP				CONTROL GROUP			
	PRIMIPARAS		MULTIPARAS		PRIMIPARAS		MULTIPARAS	
EFFECT	NO.	%	NO.	%	NO.	%	NO.	%
Normal	213	93.4	455	96.4	98	94.2	187	95.4
Labor slowed	13	5.7	14	3.0	5	4.8	7	3.6
Labor stopped	2	0.9	3	0.6	1	1.0	2	1.0

Excessive maternal sedation occurred in 5 cases (0.7 per cent) in the perphenazine group and in 7 cases (2.3 per cent) in the control group. The diminished amount of narcotic possible with perphenazine undoubtedly reduces the risk of profound maternal sedation. The perphenazine-treated patients required approximately one third less analgesia during the first postpartum day. They responded more quickly, had less nausea, and were calmer and more cooperative than the postpartum patients in the control group. The infants of the mothers who received perphenazine were less sleepy and required less medical attention for stimulation or resuscitation.

TABLE VI. EFFECT ON NEWBORN

	PERPHENAZINE GROUP		CONTROL GROUP	
EFFECT	NO.	%	NO.	%
Spontaneous respiration	621	88.7	231	77.0
Respiration within 1 minute	41	5.9	36	12.0
Apnea 1 to 4 minutes	12	1.7	18	6.0
Intubation and active resuscitation	21	3.0	12	4.0
Stillbirth	5	0.7	3	1.0
Lived; died within 24 hours	10	1.4	7	2.3
Total	700		300	

The effects of perphenazine on the newborn in the treated series are compared with the effects in the control series in Table VI. There was a higher incidence of spontaneous respiration (88.7 per cent) in infants whose mothers had received perphenazine than among the controls (77.0 per cent).

The nursing staff was impressed with the effects of perphenazine. There were fewer instances of hypotension and therefore this was of less concern to the labor room nurse. The excessively frequent linen changes and bathing which are necessary for the vomiting patient were diminished with perphenazine. The patients were calmer generally, and did not require restraint. Infants, being less narcotized, required less attention in the delivery room and after transfer to the nursery.

There were 38 women in the perphenazine-treated group and 22 in the control group who were delivered prematurely. These women usually receive less medication and therefore have more pain.

Satisfactory analgesia in the perphenazine-treated group was achieved with 5 or 10 mg. perphenazine, 50 mg. meperidine, and $\frac{1}{200}$ to $\frac{1}{100}$ grain scopolamine, and the infants exhibited no signs of excessive maternal sedation. The 38 infants who weighed less than 5½ pounds at birth included 2 sets of twins; 9 who weighed less than 4 pounds; and 9 who weighed between 4 and 5 pounds. These infants showed little or no evidence of narcosis and all but 4 responded rapidly after delivery. Two of these 4 had exhibited signs of fetal distress before delivery. There was one infant who lived 18 hours; infection and prolonged rupture of the membranes were present in the mother. In another infant, the placenta was markedly infarcted; this child never breathed spontaneously, was intubated, and died 45 minutes after birth. The third child was delivered after precipitate labor, and the fourth was stillborn from abruptio placentae prior to medication.

All patients in the premature control group received $\frac{1}{200}$ grain scopolamine, 12 received 50 to 75 mg. meperidine, and 10 received 100 mg. meperidine, 3 received a barbiturate, and 3 received tranquilizers other than perphenazine. Three of the infants weighed less than 4 pounds, 7 weighed between 4 and 5 pounds, and 12 weighed 5 to 5½ pounds. There were 3 infant deaths in this group.

Both the perphenazine-treated and control groups received low doses of opiates. An important difference between the groups is that all patients in the former category had good analgesia while in the control group analgesia was good in 11, fair in 5, and poor in 6. Because it is essential to limit opiates when the babies are premature, it is believed that this combination with perphenazine is excellent.

Summary

Perphenazine was added to the amnesia-analgesia combination administered intramuscularly to 700 obstetric patients; doses ranged from 5 to 25 mg., the usual dose being 10 mg. A control group consisted of 300 consecutive patients. All patients received meperidine and scopolamine and some received barbiturates, hypotensive agents, or oxytocin. There was a normal incidence of complications of labor.

Patients who received perphenazine and significantly lower doses of meperidine did as well as or better than those in the control group. The usual dose of 10 mg. perphenazine, 50 mg. meperidine, and $\frac{1}{200}$ to $\frac{1}{100}$ grain scopolamine proved optimal.

A most striking effect of perphenazine was a marked decrease in nausea and vomiting. Troublesome emesis occurred in 14 per cent of the control group but in only 4 per cent of the perphenazine-treated group. Perphenazine was 71.4 per cent effective in preventing nausea and vomiting.

Perphenazine was administered safely with all the commonly used anesthetic agents and with hypotensive drugs, and produced no side effects or evidence of toxicity. There was no undesired drop in blood pressure such as occurs occasionally with other phenothiazines. The amount of blood lost, the duration of labor, and the type of delivery were not influenced.

Oversedation of the mother or infant occurred less often in the perphenazine group since less opiate was needed for satisfactory relief of pain. Patients fared better and needed less analgesia during the first postpartum day. The antiemetic and tranquilizing properties of perphenazine lessened the amount of nursing service required.

The combination of medication which included perphenazine was especially suitable in premature labor. All of the 38 patients who were delivered prematurely and received perphenazine had good analgesia, but only half of the 22 similar patients in the control group had good results.

We gratefully acknowledge the cooperation during this study of the obstetrical nursing staff of Hermann Hospital.

References

1. Irwin, S., and Govier, W. M.: J. Pharmacol. & Exper. Therap. 119: 154, 1957.
2. Irwin, S., Bruckman, N., Radinger, N., Bailey, S. A., Saunders, J. C., and Kline, N. S.: Laboratory and Clinical Evaluation of Perphenazine (Trilafon). Scientific exhibit presented at a meeting of the American Medical Association, New York, 1957.
3. Irwin, S., Slabok, M., Debiase, P. L., and Govier, W. M.: Perphenazine (Trilafon), a New Potent Tranquilizer and Antiemetic: I. Behavior Profile, Acute Toxicity and Behavioral Mode of Action. (In press.)
4. Roth, F. E., Irwin, S., Eckhardt, E., Tabachnick, I. I. A., and Govier, W. M.: Perphenazine (Trilafon), a New Potent Tranquilizer and Antiemetic: II. General Pharmacology. (In press.)
5. Roth, F. E., and Winbury, M. M.: J. Pharmacol. & Exper. Therap. 119: 181, 1957.
6. Rosenkilde, H.: J. Pharmacol. & Exper. Therap. 119: 180, 1957.
7. Rosenkilde, H., and Govier, W. M.: J. Pharmacol. & Exper. Therap. 120: 375, 1957.
8. Wang, S. C.: Federation Proc. 17: 417, 1958.
9. Wang, S. C., Amols, W., and Merritt, H. H.: Neural Mechanism of Emesis and Antiemesis. Site of Action of Emetic and Anti-emetic Agents. Scientic exhibit presented at a meeting of the American Medical Association, New York, 1957.
10. Harer, W. B.: Obst. & Gynec. 11: 273, 1958.

TRANSVAGINAL PUDENDAL NERVE BLOCK— A NEW TECHNIQUE

JAMES G. LEE, M.D., KANSAS CITY, KAN.

(From Bethany Hospital)

SEVERAL articles concerning the transvaginal approach to pudendal nerve block in obstetrics have appeared in the last two years.[1, 2, 3] The earliest articles dealt mainly with the new approach, using existing equipment. Very recently articles have appeared describing different forms of needle guides to assist in the placement of the needle.

Leshock[4] describes a short guide which is attached to the finger with a ring and is introduced into the vagina at the same time as the needle. Velarde[5] describes a longer tube with a ring to encircle the index finger. This is inserted simultaneously with the hand and the needle is then introduced after the end of the tube is located against the ischial spine.

Material

Since August, 1956, a simple tube, constructed of stainless steel, large enough to admit a 20 gauge needle, has been used, and has been modified only in length since that time. The only other equipment has been a No. 20 gauge 6 inch needle and a 10 or 20 c.c. syringe (Fig. 1). During that time, pudendal block has been employed 196 times with the tube as a needle guide. An accurate account of the results of these cases has been kept in an attempt to evaluate the advantages and disadvantages of the method.

Technique

The technique has been fairly well standardized. Ten cubic centimeters of 1 per cent Xylocaine is deposited on each side posterior to the ischial spines, with the needle about parallel to the patient's spine. Two drops of 1:1,000 epinephrine is sometimes added to the Xylocaine. Hyaluronidase was used early in the series, but was abandoned when the impression was gained that it did not improve the results.

Contrary to other techniques, the left hand is used in palpating the right ischial spine and the right hand for the left side. When the spine is palpated with the middle finger, the tube is introduced between the index and middle fingers and the end of the tube is placed with the ball of the middle finger (Fig. 2). The outer end of the tube is then depressed and brought laterally as described by Kobak and associates,[1] until it is approximately parallel to the longitudinal axis of the mother (Fig. 3). After aspiration, 10 c.c. is injected on each side. When several minutes have elapsed, the labia and perineum are pinched with an Allis clamp to determine the effectiveness of the anesthesia.

The use of the hand opposite to that usually employed has two advantages. When the spine is palpated with the middle finger, the guide can be inserted between the middle and index fingers. This locates the guide inferior to the end of the spine. Also, when the left hand is used to anesthetize the left side of the patient, it is my observation that the fourth finger is inevitably contaminated on the anus. The same is true on the opposite side. This is eliminated by use of the opposite hands.

Early in the study, the impression was gained that the method made pudendal block anesthesia, definitely easier and quicker than other methods. Pudendal nerve anesthesia, however, even when complete, left something to be desired. The patient still had definite discomfort in the expulsive phase, and for this, nitrous oxide and oxygen were given with contractions and at the actual time of delivery of the head in practically all cases. The pudendal anesthesia was relied on for the episiotomy and all repair work after delivery. Intravenous morphine 0.008 Gm. was given slowly soon after delivery.

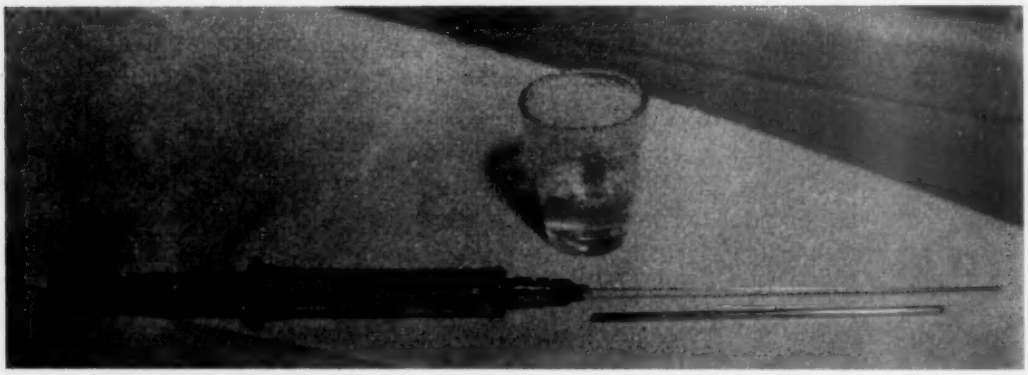


Fig. 1.—Equipment used for pudendal nerve block, showing needle guide with a 6 inch needle.

Results

If the accoucheur could perform the episiotomy and repair entirely independent of the anesthetist and without significant discomfort to the patient, the case was listed as satisfactory. If the episiotomy or repair caused discomfort but not to the point of the patient requesting additional anesthesia, the case was listed as being fair. If the patient requested additional anesthesia, the case was listed as a failure. Table I gives the results of this phase of the study.

TABLE I. RESULTS OF PUDENDAL NERVE BLOCK WITH THE USE OF TRANSVAGINAL APPROACH AND NEW TYPE OF TUBE GUIDE

	NO. OF CASES	%
Satisfactory	162	83
Fair	24	12
Failure	10	5
Total	196	100

There were numerous cases in which the anesthesia was effective on only one side. The episiotomy was performed on that side and if the patient experienced no discomfort during this or the repair, the case was listed as satisfactory. Reinjection was done in several cases because of failure on one or both sides. Seldom did the second injection improve the results.

Klink,[6] describing his transperineal approach, discussed the importance of aspirating blood from the pudendal vein. In this study, blood was aspirated only 12 times. In 2 cases it was aspirated on both sides. Anesthesia was unsatisfactory in 4 of the 12 sides in which blood was aspirated and the needle then repositioned. Blood was aspirated 4 times in one patient after the needle was moved each time. No injection was made on that side.

Fig. 2.—The middle finger is placed against the ischial spine and the guide is then introduced between the index and middle fingers.

Fig. 3.—The distal end of the needle guide is brought downward and laterally so that the needle is introduced approximately parallel to the patient's longitudinal axis.

Repair work other than the episiotomy was done in 26 cases. These procedures ranged from large extensions of the episiotomy to repair of the cervix and lacerations of the anterior vaginal wall. In this category 24 patients were classified as having good results, one fair, and one required nitrous oxide. Thus, it is felt that the anesthesia is sufficient for any repair necessary.

The duration of the anesthetic was seldom a factor once it was successful. Occasionally reinjection was necessary if delivery had not occurred when

anticipated. Results on the second injection were in all cases equal to those of the first. Since we have a definite impression that epinephrine has a tendency to slow the contractions, it is being used less frequently. Xylocaine usually is of sufficient duration.

Klink stated that if anesthesia is not evident in 3 minutes the block is probably a failure and should be repeated. In a number of cases in this study excellent results were obtained in 10 to 11 minutes, although little anesthesia had been demonstrated prior to that time.

Of the 188 patients who received a pudendal block, 12 vomited. This appears to indicate that, even though the great majority of patients received nitrous oxide, the total amount and depth of anesthesia tended to be minimal.

In the last 32 cases, the technique was changed somewhat. Five cubic centimeters was deposited beneath the ischial spines in the method described previously and then a second injection was made superiorly to the spine with the needle tilted downward. This is an attempt to decrease the percentage of failures. In this series there were 28 successes, 3 fair results, and one failure.

During the series, no attempt was made to employ pudendal nerve block in all cases. Vaginal delivery with inhalation anesthesia only was performed in 215 cases, to compare the two techniques of delivery. If any selection of cases was employed, it was toward general anesthesia at the time of delivery in the simpler cases and those in which consultations had been held. It is as a result of this experience that pudendal nerve block is being employed more frequently as time goes on.

Comment

The value and safety of pudendal block have long been recognized. The main obstacles to its wider acceptance have been the technical difficulty and the high incidence of failure, as well as the time that it takes to administer.

The transvaginal approach has obviated some of these disadvantages. The guide described here has been used by a number of operators for well over a year. It has transformed pudendal block from a very occasional procedure to one of increasing frequency.

The advantages of pudendal nerve anesthesia as observed in this series, aside from its recognized safety, can be listed as follows:

1. The great majority of patients obviously liked it.

2. There was much less moving about on the part of the patient during the repair and there was much less vomiting.

3. The only other anesthetic agent necessary was nitrous oxide and oxygen.

4. The operator can perform the episiotomy and repair independent of the anesthetist.

The advantages of a guide such as is here described are:

1. It is an easy and quick method which can be used with almost as much ease when the head is crowning.

2. The needle is much less likely to go into the glove or the vaginal mucosa while being introduced.

3. The depth of penetration of the needle can be controlled more accurately.

The disadvantages of this type of anesthesia are:

1. It is an added procedure.
2. It causes the patient some discomfort as it is administered.
3. It has a tendency to slow the second stage of labor.
4. It does not provide complete relief from pain.
5. It is not always successful.

Summary

A needle guide* is described which has been employed for 1½ years and which is believed to be a valuable adjunct in obstetrics. The technique and the results of its use are discussed.

References

1. Kobak, Alfred J., Evans, Evan F., and Johnson, George R.: AM. J. OBST. & GYNEC. 71: 981, 1956.
2. Wilds, Preston Lea: Obst. & Gynec. 8: 385, 1956.
3. Dugger, John H., Kegel, Eugene E., and Buckley, John J.: Obst. & Gynec. 8: 393, 1956.
4. Leshock, J. C.: AM. J. OBST. & GYNEC. 74: 1128, 1957.
5. Velarde, Alonso: Obst. & Gynec. 10: 687, 1957.
6. Klink, Edward Walter: Obst. & Gynec. 1: 137, 1953.

*These guides can be purchased from Munns Medical Supply Co., 1207 Grand Ave., Kansas City, Mo.

ERYTHROCYTOSIS ASSOCIATED WITH A MYOMATOUS UTERUS*

CEVAT BABUNA, M.D., G. H. GARDNER, M.D., AND R. R. GREENE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Chicago Wesley Memorial Hospital)

IN 1953 Thomson and Marson[1] reported a case of polycythemia which disappeared after surgical removal of a myomatous uterus. Subsequently there have been 4 other similar instances reported. The following case report records the sixth such case:

The patient was a 59-year-old white woman, gravida i, para i. Her last menstrual period was in 1953. She was first seen by one of us (G. H. G.) in November of 1950 at which time her hemoglobin was 12.9 grams and the red blood count was 4.1 million. In October of 1951 she was admitted to Wesley Memorial Hospital because of profuse menses and a diagnostic dilatation and curettage was performed. The histopathologic findings were "slight atrophy of endometrium" and the final diagnosis was "dysfunctional uterine bleeding." At this time the hemoglobin was 11.9 grams and the red blood count was 3.9 million. On examination under anesthesia the uterus was enlarged to about three times normal size. She was seen in the office in 1952 and 1953. The blood counts at these times were similar to those of the original examination and no changes were noted in the pelvic findings. She was hospitalized in 1954 for orthopedic reasons. At this time the hemoglobin was 14 grams and the red blood count was 4.3 million. In March of 1956 the blood counts were still normal with a hemoglobin of 15 grams and a red blood count of 4.3 million. At this time the uterus was again noted to be three times normal size. In November, 1956, 8 months after the last checkup, she was seen in the office complaining of very slight vaginal bleeding and some enlargement of the lower abdomen. At this time the counts were found to be unusually high with a hemoglobin of 18 grams and a red blood count of 6.03 million. In January, 1957, she had more spotting and the uterus was now noted to be the size of a 16 weeks' pregnancy. The hemoglobin was 20 grams per cent and the red blood count was 6.00 million.

She was admitted to Chicago Wesley Memorial Hospital on Feb. 4, 1957. General physical examination was negative. The spleen and liver were not palpable. The pelvic findings were similar to those noted in January, 1957. Her blood pressure was 160/90. X-ray showed a large well-outlined pelvic mass extending up to the fourth lumbar vertebra. The electrocardiogram, intravenous pyelogram, and chest x-ray were normal. The blood count on admission showed a hemoglobin of 20.2 grams, a red blood count of 6.17 million, and a hematocrit of 62 per cent. The white blood count was only 6,400 and the differential blood count was normal. Nonprotein nitrogen, urea nitrogen, creatinine, and the albumin-globulin ratio were normal. On Feb. 6, 1957, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The estimated total blood loss during operation was 300 c.c. The uterus was found to be soft and enlarged to the size of a 16 weeks'

*Financed in part by a cancer control grant from the National Cancer Institute of the National Institutes of Health of the Department of Health, Education and Welfare.

pregnancy. When the specimen was opened a large single submucous tumor was found (Fig. 1). It grossly suggested the possibility of a sarcoma but it was not vascular in appearance. Microscopically the tumor was found to be a "cellular" leiomyoma (Fig. 2). The ovaries were atrophic as was the endometrium.

The postoperative course of the patient was uneventful. She remained well hydrated and afebrile.

A blood volume study with radioactive iodine on the fifth postoperative day showed a plasma volume of 1,750 c.c., a red-cell mass of 1,785 c.c., and a total volume of 3,535 c.c. This showed a relative but only slight increase in the red-cell mass.

The serum bilirubin was 1.27 mg. per cent on the second postoperative day. On the sixth postoperative day it was 0.68 mg. per cent. On the eighth postoperative day it was 0.37 mg. per cent. These findings indicate that red blood cell destruction was going on on the second postoperative day.

The pre- and postoperative blood counts are shown in Fig. 3. As can be noted, the counts were still high on the first, second, and third postoperative days. On the fifth day they dropped appreciably and on the seventh day were down to normal limits with a hemoglobin of 15.3 Gm. and a red blood count of 5.3 million. Four subsequent counts after discharge from the hospital have all been within normal limits.

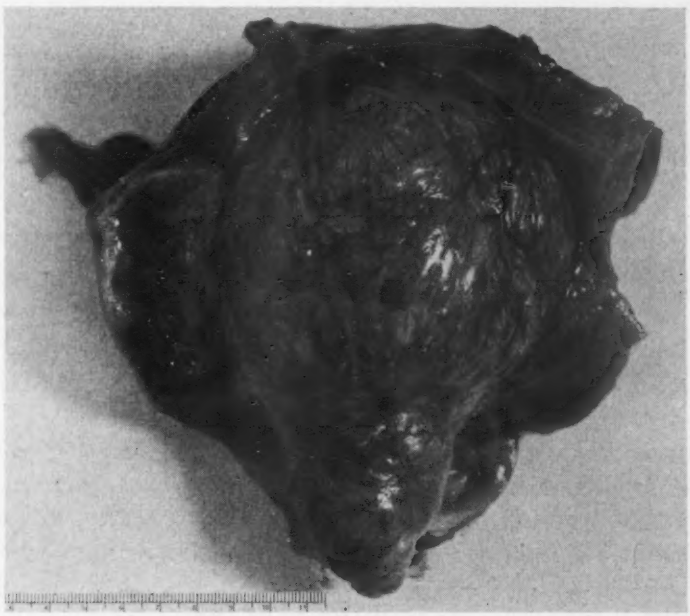
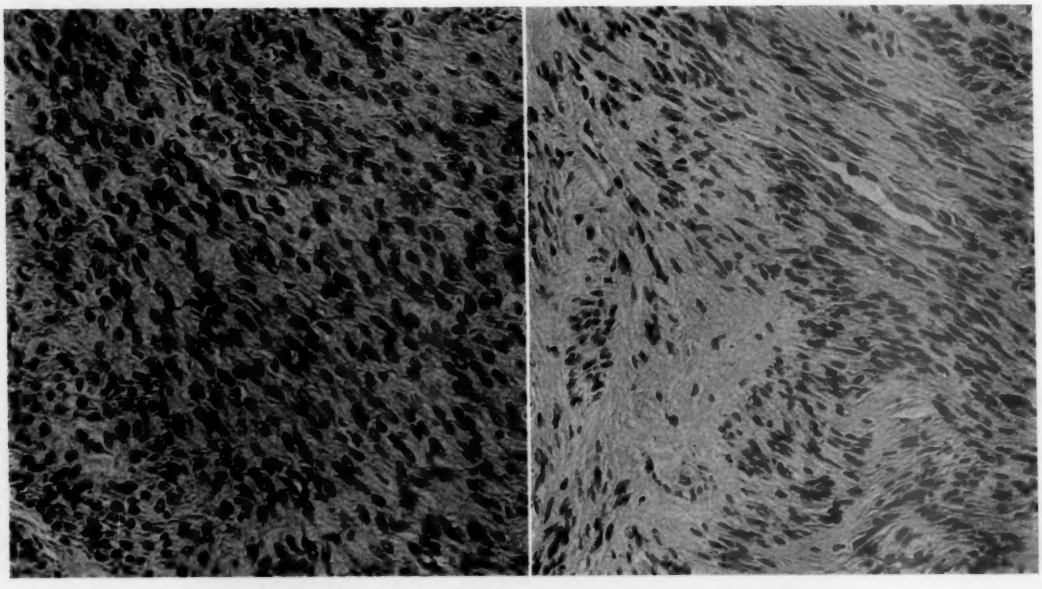


Fig. 1.—Gross specimen with uterus opened and showing the submucous tumor projecting into the endometrial cavity. The fundus is at the top and the cervix, obscured by the tip of the tumor, at the bottom.

The 5 previously reported cases are summarized in Table I. In all there was an increase in the number of red blood cells and hemoglobin which returned to normal with removal of the myoma and/or myomatous uterus. One of these patients was climacteric, another was postmenopausal, and 3 were in the menstrual age. They varied in age from 29 to 53. One was Negro, 3 were white, and the race of the other one was not reported.

There was no common characteristic in the gross findings in these tumors. One was observed to be highly vascular, another was reported as having degenerative changes. In the remaining cases nothing unusual was reported.

Through the courtesy of the authors concerned, we were able to obtain slides and/or blocks from the first 4 of these reported cases. As has been previously noted, ours was a "cellular" leiomyoma. One of the others was found to be moderately cellular. The remainder showed nothing unusual in spite of special stains.



A. *B.*

Fig. 2.—*A*, (N.U.M.S. Gyne. Path. 25938.) Shows the unusual "cellularity" of the myoma. (×125.)
B, (N.U.M.S. Gyne. Path. 13055.) A section from a myoma from a woman of comparable age (58 years) to show the usual lack of "cellularity." (×125.)

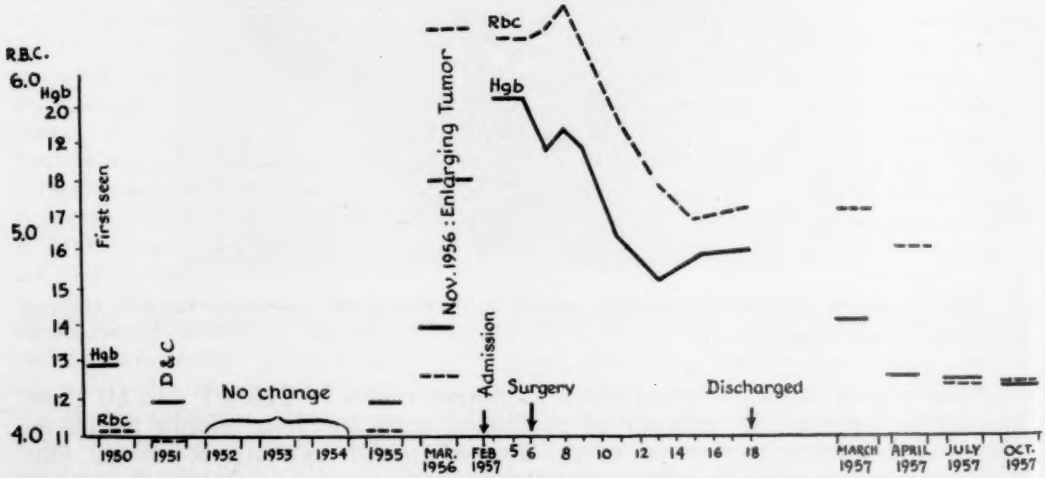


Fig. 3.—A diagrammatic reconstruction of the case history.

Comment

The patients reported upon have all been noted to have polycythemia. Their condition, however, is different from that of a patient with true polycythemia: (1) Elevated blood pressure was present in 3 out of 4 in whom it

was reported. Hypertension is very unusual in true polycythemia. (2) Normal levels of leukocytes were observed in 5 out of the 6 cases. Leukocytosis is usually present in polycythemia vera. (3) Normal spleens and livers were found in 5 out of 6 cases. Splenomegaly is an important symptom of polycythemia vera. (4) In all cases complete relief of polycythemia was obtained by the seventh postoperative day following surgical removal of uterine myomas. Such a relief cannot be obtained with polycythemia vera. Consequently all of these cases, including ours, belong to the group of so-called secondary polycythemia. It is more properly called erythrocytosis. This condition may be caused by high altitude, congenital heart disease, Ayerza's disease, chemical agents, pulmonary disease, certain tumors or disorders involving the central nervous system, hypernephroma, or Cushing's syndrome. None of these factors was present in any of these reported cases.

TABLE I

AUTHOR	TYPE OF OPERATION	RED BLOOD COUNTS		
		PRE-OPERATIVE	2-7 DAYS POST-OPERATIVE	1-92 MONTHS POST-OPERATIVE
Thomson and Marson[1]	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	7.2 million	5.5 million	4.7 million
Horwitz and McKelway[2]	Myomectomy	8.5 million	5.7 million	5.0 million
Engel and Singer[3]	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	6.0 million	5.0 million	4.3 million
Singmaster[4]	Total abdominal hysterectomy, unilateral salpingo-oophorectomy	6.3 million	3.9 million	4.9 million
Fleming and Markley[5]	Total abdominal hysterectomy, unilateral salpingo-oophorectomy	7.5 million		4.0 million

In the last case report on this subject[5] the term "myomatous polycythemia" was proposed as the name of this syndrome. Since polycythemia connotes an increase in both red blood cells and white blood cells, we do not believe this to be a fitting term; rather, we would suggest "erythrocytosis associated with uterine myomas" or "myoma-erythrocytosis syndrome."

Pathogenesis

Horwitz and McKelway, whose reported tumor was a hypervascular leiomyoma, suggested the possibility of the erythrocytosis being caused by arteriovenous shunts in the myoma. To us that explanation seems unlikely. On the other hand, there are three possibilities that might explain the development of erythrocytosis secondary to myomatous uteri. All of the theories are based on the assumption that some causative substance is secreted by the myomas. We cannot at the present time envision any other mechanism to explain this obvious (or is it only apparent?) cause-and-effect relationship.

Theories.—

1. Stimulation of the bone marrow by an internal secretion arising from the tumor. In 3 of the reported cases a mild erythropoietic activity was observed in

the bone marrow. In reality this theory is not satisfactory because if the increased red-cell count depended on simple stimulation of erythropoietic activity, the return to normal blood values could not be expected for several months, as the circulating erythrocytes would live their normal life span of 90 to 100 days. Since improvement occurred in all cases within 7 days, this theory is not satisfactory. Incidentally the differential blood count in our patient showed no evidence of unusual erythropoiesis.

2. By prolongation of the life of red blood cells. An internal secretion might act upon already circulating erythrocytes in three possible ways: (a) by decreasing their fragility, (b) by inhibiting lysolecithin enzyme which plays a role in the destruction of red blood cells, (c) by inhibitng the phagocytic activity of the reticuloendothelial blood-destroying system in the body.

Any of these mechanisms would result in an accumulation of the red cells in the circulation, i.e., an erythrocytosis. Then, as soon as this effective substance disappears, normal destruction takes place and normal counts return.

3. Inhibition of the reservoir function of the spleen. The biggest reservoir of erythrocytes in the body is the spleen. It holds a large number of cells in its vascular sinuses and can by expulsion of these red blood cells into the general circulation cause a temporary erythrocytosis in emotional stress, cold, exercise, etc. A secreted substance from the myoma might disturb this reservoir function of the spleen, resulting in a chronic erythrocytosis. As soon as this substance disappears, the spleen may again remove from circulation and store the excess erythrocytes.

It would not be very difficult to test the theories if a patient with such a condition were studied pre- and postoperatively with certain specific tests. As soon as the diagnosis of myomatous erythrocytosis is considered, the patient should have the following workup: complete blood counts and serum bilirubin, blood volume, and fragility tests, studies of the erythrocyte life span, bone marrow study, and study of the degree of the erythropoietic activity of the peripheral blood. These should be repeated in the postoperative stages.

If preoperative erythropoietic hyperactivity were demonstrated in the bone marrow and peripheral blood and disappeared postoperatively, it would indicate that the bone marrow stimulation theory may be one factor in pathogenesis—contrary to our present theoretical objection to it.

A decrease in red blood cell mass with corresponding increase in serum bilirubin level in the postoperative period, with changes in the fragility of the cells between postoperative stages, and decreased life span of erythrocytes in the postoperative stage would all definitely prove the second or inhibition of destruction theory.

If no stimulation of erythropoietic activity occurs preoperatively and no destruction can be demonstrated postoperatively, but yet the erythrocytosis disappears, then the third or spleen reservoir theory would be the only possible explanation.

It is possible that studies with extracts obtained from the fresh surgical specimens from a patient with erythrocytosis associated with a myomatous uterus

would help prove the existence of the effective substance playing the role in the development of this unusual blood picture.

Summary

The sixth instance in which a myomatous uterus apparently caused erythrocytosis has been reported. Complete and permanent relief from the increased red-cell mass and from the corresponding elevation of hemoglobin level was obtained in this and the other 5 cases by surgical removal of the myomatous tumors. No common gross or microscopic characteristic was found in the 5 specimens we were able to study personally.

Three theories are mentioned to explain the pathogenesis of this condition. An effective plan for proper study of such a case is outlined.

References

1. Thomson, A. P., and Marson, F. G. W.: Lancet **2**: 759, 1953.
2. Horwitz, A., and McKelway, W. P.: J. A. M. A. **158**: 1360, 1955.
3. Engel, H. W., and Singer, K.: J. A. M. A. **159**: 190, 1955.
4. Singmaster, Lawrence: J. A. M. A. **163**: 36, 1957.
5. Fleming, A. R., and Markley, J. C.: Am. J. Obst. & Gynec. **74**: 677, 1957.
6. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 7, London, 1957, J. & A. Churchill, Ltd.
7. Wintrobe, M. M.: Clinical Hematology, ed. 4, Philadelphia, 1956, Lea & Febiger.
8. Contopoulos, A. N., McCombs, R., Lawrence, J. H., and Simpson, M. E.: Blood **12**: 614, 1957.
9. Rodnan, G. P., Ebaugh, F. G., Jr., and Fox, M. R. S.: Blood **12**: 355, 1957.

SPONTANEOUS SUBARACHNOID HEMORRHAGE IN PREGNANCY NOT COMPLICATED BY TOXEMIA

BERNARD GOMBERG, M.D., SEATTLE, WASH.

(From The Doctors Hospital and Swedish Hospital)

SPONTANEOUS subarachnoid hemorrhage in otherwise normal pregnancy is fortunately infrequent in view of the high mortality and the frequency of neurological sequelae in those who survive. For the obstetrician it raises several important questions. Should pregnancy be discouraged or encouraged in a woman who has survived a spontaneous subarachnoid hemorrhage? If she is already pregnant at the time of the hemorrhage should therapeutic abortion be performed? If she is to be allowed to continue her pregnancy what should be the avenue of delivery?

In this presentation subarachnoid hemorrhage in otherwise normal pregnancy is specifically differentiated from hemorrhage associated with severe toxemia of pregnancy, which has a different origin and is therefore excluded from this discussion.

Material

Ten cases were admitted to The Doctors Hospital and the Swedish Hospital of Seattle, Washington, over a number of years during which 71,729 deliveries occurred at those two institutions.

CASE 1.—M. G., aged 31 years, para i, gravida ii, whose expected date of confinement was May 29, 1956, was seen on May 11, 1956, because of a sudden, severe headache, sweating, and weakness of one leg. She was a known cardiac patient with aortic and mitral valvular disease, continually maintained on digitalis, but there had been no cardiac difficulties throughout this pregnancy, or the previous one, 6 years earlier. Both the spleen and liver were enlarged and palpable from the beginning of pregnancy. The usual blood pressure ranged around 140/60, pulse 84 to 90, the urine was negative for albumin, and the total weight gain was 13 pounds. She had episodes of severe false uterine contractions for 6 to 8 weeks prior to admission and frequently complained of headaches.

The patient was admitted to the hospital immediately, where a spinal tap revealed grossly bloody fluid. By this time she was comatose; the blood pressure was 140/30 and the pulse slow and steady. After medical, neurosurgical, and obstetrical consultation it was agreed to treat the patient by conservative medical means and to ignore the pregnancy unless her condition deteriorated or labor supervened. About 12 hours later strong false uterine contractions began to disturb the patient. Rectal examination revealed no dilatation or effacement, and the presenting part was not engaged, but because the patient was becoming so restless it was decided that delivery should be effected. The fetus was estimated to be term size, and heart tones were good. Anesthesia was instituted with Pentothal sodium and cyclopropane, and rapid cesarean section followed by bilateral tubal ligation was accomplished. A 5 pound, 9 ounce male fetus in good condition was delivered. The maternal condition remained unchanged throughout the procedure.

After 2 more days of continued coma the patient began to respond to voices. A spinal tap was done with removal of 40 c.c. of grossly bloody fluid. The initial pressure was 400 mm. of water. The next day the pressure was 200 mm. of water. The patient became more alert, and attempted to respond, but unintelligibly. On May 16 she began to speak fairly well, and thereafter continued to improve slowly but complained of headaches and exhibited marked emotional instability.

On May 29, arteriograms were performed, revealing normal vessels on the right side, and normal caliber of the vessels on the left, but with elevation through the area of the middle meningeal artery and with right lateral displacement through the anterior and midportion of the course of this artery. This displacement was interpreted to be secondary to a mass having its origin in the anterior region of the temporal lobe. The patient was discharged on June 3, 1956, and did quite well for a while with almost complete recovery of function and personality. During the latter part of July, 1956, however, she began to have increasing headaches, drowsiness, confusion, right-sided weakness and hyperreflexia, and she was again admitted to the Swedish Hospital on Aug. 1, 1956, with a diagnosis of left intracerebral hematoma.

Spinal puncture showed clear fluid with normal pressure. The temporal lobe was explored by needle, and a questionable mass palpated. A ventriculogram was essentially normal. The patient did not recover consciousness after this procedure, however, and was transferred to the King County Hospital for further therapy.

On Aug. 3, 1956, the day of admission to the King County Hospital, she was taken to the operating room and a left subtemporal decompression was performed. Increased intracranial pressure was found and a large mass was palpated about 2 cm. deep to the superficial temporal cortex, which when incised released old blood. Large branches of the left middle cerebral artery were noted, and it was felt that the lesion was a large intracerebral hematoma secondary to a ruptured aneurysm. The possibility could not be ruled out, however, that this large sac was itself the aneurysm. Under the emergency conditions of the moment, it was felt that a decompression was the most that could be safely accomplished, and that if the patient survived, future studies would indicate the possibility of further definitive treatment.

The patient had a slow but steady recovery, and is relatively well except for a residual right hemiparesis, aphasia, and personality changes. Some improvement has been accomplished with physiotherapy and speech training. Angiographic study of the left carotid artery after recovery from the decompression operation failed to reveal an aneurysm.

CASE 2.—V. W., aged 27 years, para i, gravida ii, whose expected date of confinement was May 4, 1949, was admitted to the Swedish Hospital on March 4, 1949, complaining of a severe frontal headache with some occipital radiation, and persistent nausea and vomiting of all food and fluids taken, which had begun 12 hours prior to admission. There had been no disorientation or loss of consciousness. Her general health and the pregnancy until that time had been normal, as were the past history and previous pregnancy.

Physical examination showed a normal 7 months' gestation. There was nuchal rigidity but no impairment of mental function. The blood pressure was 120/70 and the pulse 102. The heart, lungs, funduscopic examination, and reflexes were all normal. The spinal fluid was uniformly bloody with a pressure of 120 mm. of water. Blood counts and urinalysis were normal for pregnancy.

The hospital course on conservative medical management was fair, with nausea and vomiting gradually subsiding until by March 18, 1949, she was on a full diet again. The only remaining symptom was a dull headache, but neurological examination was always normal. On March 22, 1949, at 11:55 A.M. she suddenly developed a generalized clonic convulsion which was persistent for 15 minutes until 0.25 Gm. Pentothal was given intravenously. The pulse was 66, and blood pressure 170/80. She had respiratory difficulty and rhonci were heard throughout the lung fields. The pupils were markedly dilated. The spinal fluid was grossly bloody with a pressure of 600 mm. of water. It was reduced to 180 mm. of water. At 4:55 P.M. respirations stopped and at 5:00 P.M. the heart stopped despite artificial respiration and injection of 0.5 c.c. of 1:1,000 Adrenalin into the apex. The fetal heart stopped at 5:20 P.M.

Autopsy disclosed an intrauterine pregnancy of 7 months' duration, and an intracranial hemorrhage of the right frontoparietal area, with rupture into the right lateral ventricle. (The exact source of the hemorrhage could not be identified.)

CASE 3.—A. D., aged 26 years, para 0, gravida i, approximately five months pregnant, was admitted to The Doctors Hospital at 12:45 A.M. on July 4, 1956, complaining of the sudden onset of severe headache, neck and back pain, 3 hours prior to admission. The patient had been well prior to this episode. The blood pressure was 116/70. The impression was that this was a hysterical reaction, but that she should be observed for symptoms of meningeal irritation. She was given Demerol 50 mg. intramuscularly at 1:00 A.M. followed by emesis. At 1:10 A.M. she was given 50 mg. Marezine intramuscularly. She stated that the pain was so severe that unless relieved she was going to die. At 1:30 A.M. she was given Seconal, 2 grains hypodermically. She continued to awaken at intervals and to moan and thrash about. At 4:30 A.M. Demerol, 50 mg. intramuscularly, was repeated. She became incontinent and held her head arched backward. At 8:00 A.M. the rectal temperature was 101° F., pulse 112, respirations 26. She was no longer responsive and there was intermittent twitching of the hands. At 9:45 A.M. she died.

Autopsy showed a 5 months' intrauterine gestation and a ruptured aneurysm of the basilar artery.

CASE 4.—P. R., aged 27 years, a primigravida, 35 weeks pregnant, was admitted to The Doctors Hospital on Feb. 28, 1948, at 5:30 A.M. following the spontaneous onset of labor. Pregnancy had been normal except for edema of the ankles. Delivery of normal female twin infants was effected at 6:15 A.M. Following the delivery, the patient awakened from the anesthesia and appeared to be in good condition. One hour following delivery she complained of headache which persisted. Empirin was given and subsequently she vomited. Four hours after delivery she suddenly had a convulsion and became unconscious and cyanotic. This episode lasted approximately 10 minutes. Following the convulsion the patient remained comatose. The right side of the face and entire right side of the body were paralyzed. The blood pressure, which was 146/90 following delivery, was 156/90 immediately after the convulsion and 190/120 2 hours afterward. Urinalysis on admission showed 2 plus albumin, but a urine specimen taken following the convulsion was negative for albumin. An intravenous sucrose solution was administered. On examination 4 hours after the initial convulsion the tendon reflexes on the right side appeared hyperactive with positive Hoffmann and Babinski signs. A spinal tap was then performed, yielding bloody fluid under an initial pressure of 185 mm. of water showing normal dynamics. The patient was then placed in an oxygen tent and given vitamin K. Serial blood pressure readings showed a drop to 120/100 6 hours after the initial convulsion with a subsequent rise to 170/120 10 hours later. There were repeated small convulsions. A transfusion of whole blood was given. A second spinal tap yielded fluid similar to that obtained on the first puncture. Death occurred approximately 12 hours after the first convulsion from apparent respiratory failure.

Autopsy revealed a fresh cerebral hemorrhage of the left frontoparietal area, but the source of hemorrhage could not be identified.

CASE 5.—E. P., aged 35 years, para i, gravida ii, at term, was admitted to the Swedish Hospital for induction of labor on July 13, 1956. Pitocin was administered with glucose in water intravenously and after a 5½ hour labor, under ethylene anesthesia, a normal fetus was delivered by low forceps over a midline episiotomy. The patient did not awaken or respond following delivery, and 4½ hours later the left arm and both legs were noted to be spastic. The blood pressure was 160/80, the pupils were round and equal, but showed no light reflex. In another 30 minutes slight responses were elicited and spasticity was no longer present. The neurological consultant considered this to be a case of subarachnoid hemorrhage, but no diagnostic studies were done. The patient improved gradually and was discharged on Aug. 10, 1956, with weakness of the right arm and impaired walking.

CASE 6.—E. K., aged 20 years, a primigravida, was admitted to The Doctors Hospital on March 5, 1955, with a 5½ months' pregnancy complicated by a subarachnoid hemorrhage.

She improved and was transferred to the Swedish Hospital on March 21, 1955, for angiograms which were suggestive of a small aneurysm just proximal to the bifurcation of the left internal carotid artery. The neurological consultant advised cesarean section at term. The patient was discharged from the hospital on March 27, 1955, and was delivered at term by elective cesarean section. She has remained well subsequently.

CASE 7.—R. P., aged 35 years, para iv, gravida ix, at term, was admitted to the Swedish Hospital for elective cesarean section. At about the third month of pregnancy the patient had been in another hospital with a clinical diagnosis of ruptured cerebral aneurysm from which she recovered without surgical treatment. Cesarean section delivery of a normal 6 pound female infant was performed, followed by tubal ligation. Spinal anesthesia was utilized, with administration of Vasoxyl and ephedrine before and during operation. Pitocin was injected into the uterus. The patient has remained well.

CASE 8.—D. C., aged 25 years, para ii, gravida iii, had a subarachnoid hemorrhage in October, 1955, from which she recovered without surgical treatment. She was admitted to the Swedish Hospital on Jan. 10, 1956, for interruption of a 2 months' pregnancy because of the previous subarachnoid hemorrhage. She has remained well.

CASE 9.—G. P., aged 34 years, was admitted to The Doctors Hospital and a therapeutic abortion for malignant hypertension was attempted, which was not successful and was repeated one month later. Five days later she had a subarachnoid hemorrhage, and died. Autopsy revealed a ruptured small aneurysm of the basilar artery.

CASE 10.—J. O., aged 22 years, para i, gravida ii, was admitted to The Doctors Hospital in 1953 with a subarachnoid hemorrhage and a 10 weeks' pregnancy for which a therapeutic abortion was performed. Recovery was good and several months later she again became pregnant (because of a failed sterilization of her husband) and abortion was again performed. Since then she has been well.

Comment

Incidence.—In 9 of the 10 cases comprising this study subarachnoid hemorrhage occurred during pregnancy or shortly afterward, an incidence of 1:7,970 deliveries. Cannell and Botterell[1] estimated somewhat less than 1:2,000, while de Carle[2] found 1:5,139 deliveries. Moskowitz and Schneider[3] believed that subarachnoid hemorrhage with pregnancy occurs more often than is appreciated because of the failure to recognize it, while Walton[4] reported no increased frequency as a result of pregnancy.

Cause of Hemorrhage.—In 3 of the 10 patients in this report ruptured intracranial aneurysm was definitely demonstrated, and in 3 others an aneurysm was strongly suspected but not proved. In the remaining 4 the cause was not determined. Aneurysmal origin for the subarachnoid hemorrhage is shown by angiography, surgical exploration, or at necropsy. That an aneurysm as the source of the bleeding cannot always be definitely identified is not surprising in view of the fact that before rupture these defects are mostly from 4 to 10 mm. in size.[5]

The great majority of subarachnoid hemorrhages (perhaps 80 per cent)[4, 5, 6] are due to ruptured intracranial aneurysms, while some cases are caused by an arteriovenous aneurysm or a blood-vessel tumor, such as an angioma. Cannell and Botterell[1] reported 16 cases in pregnancy, of which 6 were caused by ruptured intracranial aneurysms, 3 by arteriovenous malformations, 3 by undetermined causes (probably aneurysms), and one by mycotic aneurysm; 2 were associated with pre-eclampsia and 1 with thrombosis of the superior sagittal sinus.

Russell[7] pointed to ruptured aneurysm as the most common cause of spontaneous subarachnoid hemorrhage between the ages of 20 and 40 years. In the present cases the youngest patient was 20 and the oldest was 35 years of age.

These lesions are for the most part congenital in origin. Their exact mode of formation is beyond the scope of this discussion, but the congenital defect is thought to be either a weakness of the muscular layer of the artery at its point of bifurcation, or an absence of the internal elastic membrane, or both. Aneurysms may also be arteriosclerotic, mycotic, or syphilitic in origin.[8]

Intracranial aneurysms may be associated with other congenital anomalies, and particularly with congenital polycystic kidney disease.[9] Brown[10] reported that although intracranial aneurysm is found in about 1 per cent of routine autopsies for all causes, it is found in 16 per cent of the cases with polycystic kidneys; and, conversely, while in 0.3 per cent of postmortems polycystic kidneys are found, they are present in 4 per cent of autopsies done for intracranial aneurysms. No congenital defects were recognized in these patients.

Site of Hemorrhage.—The blood vessels concerned most often are components of the circle of Willis system or its branches.[7, 11] Most studies indicate that the majority of aneurysms arise from the anterior half of the circle of Willis, Hanberry[8] finding 75 per cent from the anterior and 25 per cent from the posterior half. Martland,[9] however, found a uniform distribution over the circle of Willis.

Stage of Pregnancy.—Of the 9 patients in this series who were pregnant at the time of the subarachnoid hemorrhage, the accident took place in 2 during or immediately after delivery (22 per cent), during the third trimester in 2 (22 per cent), in the second trimester in 2 (22 per cent), and during the first trimester in 3 (33 per cent). This is made more significant by combining the cases which occurred during the final trimester with those in labor (44 per cent), or by combining those of the entire second half of pregnancy (67 per cent).

Physiological changes in maternal circulation during the second half of pregnancy might be expected to contribute to a higher incidence of subarachnoid hemorrhage during that time. There is an increase in blood volume, reaching its peak in the last trimester, and an even proportionately greater increase in cardiac output.[12] The cardiac minute volume always increases during work, but more in the pregnant than in the nonpregnant state.[13] The blood pressure decreases from the fourth through the ninth lunar months, but increases in the tenth month, accompanied by an increased pulse pressure.[6, 14] During labor the blood pressure increases until after the third stage, and during contractions is 5 to 10 mm. higher than betwen them.[12] A personal communication from Caldeyro to Cannell and Botterell[1] reports a significant elevation of blood pressure with uterine contractions. An increase in pulse rate occurs when the patient bears down during contractions, and may exceed 110 per minute in 10 per cent of patients.[12] From a physiological viewpoint, therefore, pregnancy and labor may work to the disadvantage of the patient with an intracranial vascular anomaly.

Walton,[4] although stating that there is no increase in frequency of subarachnoid hemorrhage as a result of pregnancy, or any particular period of pregnancy, presents figures which show that 31.5 per cent occurred after delivery (19 per cent within 24 hours of delivery), 12.5 per cent during labor, and 56 per cent prior to labor (but usually in the third trimester or late second trimester). Thus, even if as much as 24 hours is allowed for labor, *31 per cent* occurred in a span of 48 hours, which represents substantially less than *1 per cent* of the average duration of pregnancy. Schwartz[15] holds a similar view but his figures indicate that almost half of his cases began during the short span covered by labor and the first 24 hours post partum. Others[11, 16, 17] have reported an increased frequency late in pregnancy, during labor, or in the early puerperium. These various figures seem to indicate somewhat more than a coincidental, or chance, relationship.

Prognosis.—In this study 4 of the 10 patients died (40 per cent), 2 recovered, with neurological deficits, and 4 apparently recovered completely. The mortality is generally accepted as around 50 per cent. According to Hamby[18] 45 per cent die in the initial attack. With a single episode of bleeding 62 per cent recover, but with multiple episodes only 34.5 per cent recover. Walton[4] reviewed 1,300 cases with a mortality of 45 per cent, and of those who recovered 10.5 per cent had another attack within 6 months. Jacobson[19] found a 40 to 50 per cent mortality through the first year; 28 per cent died in the first attack. Hanberry[8] also found a 50 per cent mortality, half in the first 48 hours, and half in the next 6 to 8 weeks, with 30 per cent of the survivors eventually having a recurrence with a mortality rate higher than for the first attack. He also noted that women had a higher rate of recurrence than men.

That coma is a bad omen seems undisputed.[11, 15, 16, 19] Poor prognostic signs listed by Jacobson are coma, convulsions, hypertension, and papilledema, in that order. According to Schwartz 100 per cent died when unconsciousness was the initial symptom, and 86 per cent died when it supervened.

In Walton's 32 cases in pregnancy there was a 40 per cent mortality, but in the 10 cases that occurred either during labor or in the first 24 hours post partum there was a 50 per cent mortality.

Treatment.—Treatment is of two general types, nonsurgical and surgical. The former consists of absolute bed rest and sedation to avoid excitement and elevation of blood pressure. Spinal taps may be done to relieve increasing intracranial pressure,[8] but removal of too much fluid is to be avoided. Usually 15 to 20 c.c. may be drained slowly so as to diminish the spinal fluid pressure by no more than half of the initial value.[15]

There are a number of varieties of surgical therapy.[20] These include ligation of the common carotid artery or the cervical portion of the internal carotid on the affected side, which carries with it some risk of hemiplegia, while not eliminating the danger of recurrent hemorrhage. On the other hand, intracranial clipping or ligation is attended by a high operative mortality because of the danger of bursting the aneurysm, but recurrence in the successful cases is almost zero.[7] Trapping of the aneurysm, when feasible, seems most desirable.[8]

Any definitive surgical procedure is practicable, however, only when the lesion can be demonstrated, and in the opinion of Jacobson, in only about 50 per cent of cases of subarachnoid hemorrhage can an aneurysm be shown. In addition, 13 per cent of patients with an aneurysm have multiple aneurysms, and this is considered to be a contraindication to surgery,[19] as is coma, or evidence of extreme neurological damage,[1] or the acute bleeding stage.[21] Therefore, successful surgery may be contemplated in less than 50 per cent of all cases. On the other hand, when surgical therapy for the subarachnoid hemorrhage is indicated there is agreement that pregnancy should not be a contraindication.[1, 4, 6, 17, 22]

The obstetrical management of the patients in this report was rather uniform. There were no vaginal deliveries following known subarachnoid hemorrhage in this series. Three patients were delivered by cesarean section in order to avoid labor. One of these operations was done the day following the subarachnoid hemorrhage because of disturbing uterine contractions with a 37 weeks' pregnancy. The other 2 were done at term following recovery from subarachnoid hemorrhage which occurred at 3 months in one and 5½ months in another. Two cases received no special obstetrical management since they occurred during or following labor; 2 patients died undelivered at 5 and 7½ months. One early pregnancy was interrupted because of the occurrence of subarachnoid hemorrhage, and 2 were interrupted because of subarachnoid

hemorrhage with recovery prior to this pregnancy. One subarachnoid hemorrhage and death occurred following therapeutic abortion for another cause. As might be anticipated, there is no such uniformity in the reports in the literature concerning the method of delivery and the desirability of interrupting a pregnancy or of preventing future pregnancies.

The best method of delivery for all patients with lesions not treated successfully by surgery seems logically to be elective cesarean section as was accomplished in Cases 1, 6, and 7 of this report. Cesarean section is advocated by Walton[4] for patients in whom the bleeding occurred within the last 2 or 3 weeks of pregnancy since there is not sufficient time for the lesion to heal. One patient (Case 1) was so treated. Elective cesarean section for maternal indication is the procedure of choice of Feldman, Gross, and Wimpfheimer,[6] Sullivan and associates,[16] Conley and Rand,[17] Garber and Maier,[23] Moskowitz and Schneider,[3] and Johnson.[24] Cesarean section may also be required to save the child.[4, 16] Sullivan and his co-workers[16] used the fetal prognosis as well as the maternal as a guide to obstetrical management, and they concluded that for the sake of both the mother and the fetus delivery by cesarean section is advisable as soon as possible after 36 weeks. They showed that with coma there was a 75 per cent maternal mortality and 38.5 per cent fetal mortality, while there were neither maternal nor fetal deaths among patients without coma. Their over-all incidence of coma when subarachnoid hemorrhage occurred during pregnancy was 66 per cent, but from 36 weeks through the immediate puerperium it was 86 per cent, and this was also the period of pregnancy in which 70 per cent of the subarachnoid hemorrhages occurred.

On the other hand, Cannell and Botterell[1] reserve cesarean section for obstetrical indications only, with the possible exception of the cases in which the source of the bleeding is undetermined or inaccessible and the bleeding has occurred immediately prior to or during labor. Schwartz[15] and Speck[25] also stated that cesarean section should be performed for obstetric indications alone. Walton[4] believed most patients should be delivered vaginally, by forceps, under good sedation. Decker and Rowe[22] performed a vaginal delivery in one patient after successful surgical treatment of the hemorrhage. Feldman, Gross, and Wimpfheimer[6] felt that vaginal delivery with terminal caudal anesthesia is acceptable for patients already in rapidly progressing labor. The use of oxytocics may produce harm in patients of this type,[3, 6, 15] and anesthesia should be carefully selected in order to avoid hypertension and vomiting.[6]

Interruption of an early pregnancy to avoid recurrent subarachnoid hemorrhage (Cases 8 and 10) seems warranted since Sullivan[16] has shown that *70 per cent* of the cases occurred from the thirty-sixth week through the immediate postpartum period, which represents approximately *10 per cent* of the duration of the pregnancy. This suggests that something about that stage of pregnancy increases the incidence, since it is reasonable to assume that the incidence during the first half of pregnancy would not be lower than in the nonpregnant woman. To put it another way, it seems likely that avoidance of the last 10 per cent of the gestational period would of necessity reduce the incidence of subarachnoid hemorrhage, or at least postpone it. Others[2, 6, 13, 26] also advocate intervention.

Contrarywise, Walton[4] sees no justification for termination of pregnancy since he believes that the prognosis is not affected by pregnancy, labor, or the puerperium, and others[1, 15, 25] agree. If the subarachnoid hemorrhage occurs in the earlier stages of gestation and is successfully treated by surgery, or occurs later in pregnancy with good recovery, it seems acceptable to permit the pregnancy to continue to term, as was done in Cases 6 and 7 of the present report.

The concern over future pregnancies in patients who have had spontaneous subarachnoid hemorrhage is a real one. Granted that the underlying cause of the hemorrhage is present prior to pregnancy and that the likelihood of eventual hemorrhage therefore is high regardless of gestation, and granted that the mortality from the accident is not increased because of the coincidence of pregnancy, it still seems desirable to postpone as long as possible a condition which carries such a high mortality. Hence, if pregnancy does increase the danger of hemorrhage, it appears justifiable to avoid it when the causative mechanism is known to be already present. In this series tubal sterilization was performed in 2 cases at the time of cesarean section (Nos. 1 and 7) and in one instance (No. 10) the husband was sterilized. Opposition to future pregnancies in such patients is expressed by several authors,[2, 6, 17, 26] but Walton[4] and Speck[25] disagree, finding no contraindication to future pregnancies if recovery from the subarachnoid hemorrhage is good.

Summary

Ten cases of subarachnoid hemorrhage in association with pregnancy have been analyzed and the literature reviewed in an attempt to determine whether or not future pregnancies should be interdicted, whether or not present pregnancies should be interrupted, and the method of delivery to be used if they are allowed to continue. While there is no uniformity in the literature, these 10 cases were handled fairly uniformly, and certain principles emerge from the analysis. Avoidance of future pregnancies and interruption of early pregnancies, except in cases successfully treated surgically, seem justifiable. After the first trimester the pregnancy may be allowed to continue, but should be delivered electively as soon after 36 weeks as feasible, and by cesarean section, unless successful surgical treatment of the lesion has been carried out.

References

1. Cannell, D. E., and Botterell, E. H.: Am. J. Obst. & Gynec. **72**: 844, 1956.
2. de Carle, D. W.: West. J. Surg. **57**: 181, 1949.
3. Moskowitz, H. L., and Schneider, H.: Am. J. Obst. & Gynec. **36**: 489, 1938.
4. Walton, J. N.: Brit. M. J. **1**: 869, 1953.
5. Richardson, J. C., and Hyland, H. H.: Medicine **20**: 1, 1941.
6. Feldman, R. L., Gross, S. W., and Wimpfheimer, S.: Am. J. Obst. & Gynec. **70**: 289, 1955.
7. Russell, J. R.: J. Indiana M. A. **49**: 511, 1956.
8. Hanberry, J. W.: Stanford M. Bull. **13**: 317, 1955.
9. Martland, H. S.: Am. J. Surg. **43**: 10, 1939.
10. Brown, R.: Glasgow M. J. **32**: 333, 1951.
11. Pedowitz, P., and Perell, A.: Am. J. Obst. & Gynec. **73**: 736, 1957.
12. Greenhill, J. P.: Obstetrics, Philadelphia, 1955, W. B. Saunders Company.
13. Christensen, E., and Larsen, H.: Acta psychiat. et neurol. scandinav. **29**: 441, 1954.
14. Cohen, M. E., and Thomson, K. J.: J. A. M. A. **112**: 1556, 1939.
15. Schwartz, J.: Am. J. Obst. & Gynec. **62**: 539, 1951.
16. Sullivan, C. L., Minkel, H., Campbell, E., and Graham, J. H.: Postgrad. Med. **14**: 329, 1953.
17. Conley, J. W., and Rand, C. W.: A. M. A. Arch. Neurol. & Psychiat. **66**: 443, 1951.
18. Hamby, W. R.: J. A. M. A. **136**: 522, 1948.
19. Jacobson, S. A.: A. M. A. Arch. Neurol. & Psychiat. **72**: 712, 1954.
20. Cleveland, D., and Swart, R. E.: Wisconsin M. J. **55**: 528, 1956.
21. Williamson, W. P., and Brackett, C. E.: Am. Surgeon **22**: 100, 1956.
22. Decker, A., and Rowe, E. C.: Am. J. Surg. **85**: 561, 1953.
23. Garber, M., and Maier, R. R.: Am. J. Obst. & Gynec. **56**: 1174, 1948.
24. Johnson, C. S.: M. Ann. District of Columbia **21**: 585, 1952.
25. Speck, G.: Virginia M. Monthly **81**: 270, 1954.
26. Rhoads, E. E.: Am. J. Obst. & Gynec. **54**: 533, 1947.

PERPHENAZINE SUPPOSITORIES* IN NAUSEA AND VOMITING OF PREGNANCY

CHARLES H. BIRNBERG, M.D., ALBERT A. SCHWARTZ, M.D., AND SEYMOUR WIENER, M.D., BROOKLYN, N. Y.

(From the Brooklyn Jewish Hospital)

THE phenothiazine derivatives are extremely valuable in medical practice because of their dual ability to reduce anxiety and control emesis. Chlorpromazine,[1, 2] the first of these agents to be introduced, proved to be very effective; certain fairly serious side effects[3] associated with its use, however, provoked further manipulation of the phenothiazine radical to obtain increased potency and reduced side effects. Newer analogues such as promethazine,[4] promazine,[5] mepazine,[6] prochlorperazine,[7] and perphenazine[8] are now available.

Some of these agents are widely used in the symptomatic treatment of emesis of organic and functional origin. Wang and colleagues[9] suggest that these agents act by competing with endogenous or exogenous emetic substances at the chemoceptive emetic trigger zone, thus blocking the impulse before it reaches the vomiting center.

Rosenkilde and Govier[10, 11] tested several phenothiazines for their ability to protect against apomorphine-induced vomiting in dogs; they found that perphenazine was most effective in this respect and demonstrated approximately 24 times the antiemetic potency of chlorpromazine. The antiemetic effectiveness of perphenazine, administered orally or by injection, was confirmed clinically, although in the human the potency ratio of perphenazine to chlorpromazine is approximately 6 : 1.[12]

Ernst and Snyder[12] treated 201 patients, of whom 35 had emesis of organic origin and the balance had anxiety states associated with gastrointestinal symptoms. Favorable results occurred in 162. These authors consider perphenazine especially valuable in cases of nausea and vomiting with an emotional component. On doses of 8 to 24 mg. daily, side effects were minimal and there was no laboratory evidence of pathologic change even after treatment for as long as 7 months.

Moore and colleagues[13] conducted a carefully controlled double-blind study among over 600 patients who received perphenazine by injection to prevent postoperative vomiting. Half of these patients received 15 mg. in 4 doses

*Supplied as Trilafon Suppositories by the Schering Corporation, Bloomfield, N. J., through the courtesy of J. Black, M.D.

during 24 hours; the other half received injections of the solvent only. Statistically significant results occurred: 18 per cent of the patients who received the placebo vomited, while only 6 per cent of the patients treated with perphenazine vomited.

Preisig and Landman[14] treated 32 hospitalized patients with injections of 5 mg. perphenazine to control nausea and vomiting of organic origin. All but one patient experienced relief lasting for 12 hours. These authors also reported a series of 103 office patients with tension and anxiety; perphenazine produced marked relief in 74.

Weiss and colleagues[15] used 12 to 24 mg. of perphenazine, administered orally, in 110 patients with nausea and vomiting of organic origin, obtaining good results without significant side effects in nearly all.

Recently perphenazine in suppository form was made available for clinical research. This study reports an evaluation of this agent in nausea and vomiting of pregnancy.

Method

This series consists of 67 office patients ranging in age from 18 to 39 years, the average being 28 years. Symptoms, which began during the second to the fifth week of pregnancy, were severe in 22 patients, moderate in 31, and mild in 14. At the time of treatment 26 patients were in the first trimester of pregnancy, 31 in the second, and 10 in the third. Thirty-one patients were gravida i; 24, gravida ii; 6, gravida iii; 4, gravida iv; one, gravida v; and one, gravida vi.

Suppositories containing 8 mg. perphenazine were prescribed for administration before bedtime and upon awakening. A few patients who experienced side effects on this dosage were instructed to halve the suppositories for each administration. Treatment was continued as long as necessary, which amounted to one week for 2 patients, 2 weeks for 10, 3 weeks for 22, 4 weeks for 11, 5 weeks for 8, 6 weeks for 6, 7 weeks for one, and 8 weeks for 2. The full duration of treatment is not known at this writing in 5 patients who are still taking perphenazine.

A double-blind study was conducted among 12 office and 10 clinic patients whose histories and symptoms were similar to those described above. Fifty-one trials were made, with the active drug used 12 times and indistinguishable placebos 39 times. None of the investigators knew which drug was administered until all results were recorded and the code was broken.

Results

The suppositories proved to be strikingly effective: 56 (84 per cent) of the 67 patients were completely relieved of nausea and vomiting. The drug took effect rapidly (usually within 30 minutes) and its effect was long lasting; symptoms were fully controlled during the hours when emesis usually occurred.

The medication was in general very well tolerated. Eighteen patients (27 per cent) experienced mild side effects on 16 mg. daily; these effects were eliminated or substantially reduced when dosage was halved. Nine patients reported drowsiness, 3 were dizzy, and 6 were drowsy and dizzy. None of our patients experienced the Parkinsonian tremor which has been reported by some authors[8, 12] following administration of perphenazine, and none exhibited side effects, such as agranulocytosis, hypotension, and jaundice, which occur fairly frequently with some other phenothiazines.

Favorable effects also were evident during the double-blind study. In the 12 trials with perphenazine, positive results occurred 9 times (75 per cent); in the 39 trials with the placebo, positive results occurred 9 times (23 per cent). The effects of perphenazine were so marked that in most instances the examiner could guess correctly whether the active or the inert suppository had been administered.

Comment

Originally it was planned to continue the double-blind study until there were sufficient data to permit analyses of statistical significance; however, practical considerations warranted termination of the experiment after relatively few trials. The obvious effectiveness of perphenazine made it difficult to withhold medication from the acutely uncomfortable patients who expected relief.

The patient-doctor relationship is a significant element in the treatment of nausea and vomiting of pregnancy, and this factor accounts for the placebo effect which occurred in 23 per cent of the patients who received the inert material. The favorable therapeutic climate also influenced results in patients who received perphenazine; however, the significantly inferior result among the control series indicates that perphenazine exerts a true drug effect beyond any placebo effect.

Experience showed the impossibility of separating the psychic (tranquilizing) from the physical (antiemetic) action of perphenazine since both physical and psychological factors operate to produce nausea and vomiting of pregnancy. Perphenazine appears to be the drug of choice to treat both components.

The suppositories are the ideal means of administration in this indication. Oral medication, particularly if emesis is severe, often is not retained; even more important is the fact that in pregnant patients anything taken by mouth is likely to initiate nausea and vomiting. Injections are not feasible in patients who require daily dosage for several weeks.

Summary and Conclusion

Suppositories containing 8 mg. perphenazine were administered twice daily to 67 office patients with nausea and vomiting of pregnancy. The usual duration of treatment was 3 weeks but some patients used this agent for 8 weeks or longer.

Symptoms were perfectly controlled in 56 (84 per cent) of the patients. Mild side effects (dizziness and/or drowsiness) occurred in 18 (27 per cent) of the patients and were reversed by halving dosage.

A double-blind study among 22 patients confirmed the efficacy of perphenazine objectively.

Perphenazine in suppository form appears to be the agent of choice in controlling nausea and vomiting of pregnancy, because of its rapid absorption, prolonged action, and freedom from serious side effects.

References

1. Moyer, J. H., Kinross-Wright, V., and Finney, R. M.: A. M. A. Arch. Int. Med. **95**: 202, 1955.
2. Moyer, J. H., and others: Am. J. M. Sc. **227**: 283, 1954.
3. Stein, A. A., and Wright, A. W.: J. A. M. A. **161**: 508, 1956.
4. Howarth, S., and Owen, S. G.: Brit. M. J. **2**: 1266, 1954.
5. Fazekas, J. F., et al.: J. A. M. A. **161**: 46, 1956.
6. Gold, M. I., and Stone, H. H.: Anesthesiology **18**: 357, 1957.
7. Vischer, T. J.: New England J. Med. **256**: 26, 1956.
8. Cahn, C. H., and Lehmann, H. E.: Canad. Psychiat. A. J. **2**: 104, 1957.
9. Wang, S. C., Amols, W., and Merritt, H.: Neural Mechanism of Emesis and Anti-emesis. Site of Action of Emetic and Anti-emetic Agents, Scientific exhibit presented at a meeting of the American Medical Association, June, 1957.
10. Rosenkilde, H.: J. Pharmacol. & Exper. Therap. **119**: 180, 1957.
11. Rosenkilde, H., and Govier, W. M.: J. Pharmacol. & Exper. Therap. **120**: 375, 1957.
12. Ernst, E. M., and Synder, A. M.: Pennsylvania M. J. **61**: 355, 1958.
13. Moore, D. C., et al.: Anesthesiology **19**: 72, 1958.
14. Preisig, R., and Landman, M. E.: Am. Pract. & Digest Treat. **9**: 740, 1958.
15. Weiss, S., Weiss, J., and Weiss, B.: Am. J. Gastroenterol. **29**: 173, 1958.

191 Ocean Avenue (Dr. Birnberg)

AN OBSTETRICAL FORCEPS WHICH USES A NEW PRINCIPLE OF PARALLELISM*

WALLACE B. SHUTE, B.A., M.D., M.R.C.O.G., F.R.C.S.(C),
OTTAWA, ONTARIO

THOUGH the principle of delivery by traction was described by Hippocrates and demonstrated by Avicenna in the eleventh century, it remained for the contentious but brilliant Peter Chamberlen to develop the first humane obstetrical forceps known to the western world. Since 1723, when the jealously guarded secret of his instrument was finally revealed to the profession, all modifications of Chamberlen's prototype (and there have been over 600 of these!) have been designed to increase the safety or ease of application of these forceps.

During the last 250 years four major alterations of Chamberlen's pattern have been introduced:

1. The addition of a pelvic curve to the forceps blade by Levret in 1747.

2. The invention of the English lock by Smellie in 1752.

3. The introduction of the principle of axis traction by Tarnier in 1877 to facilitate passage of a high head through the curve of Carus.

4. The modifications of Kielland. He incorporated a sliding lock for application to the asynclitic head and, by eliminating the pelvic curve completely to permit easy rotation from transverse positions, returned directly to the straight blade of the first forceps model.

Further minor modifications include the Barton forceps which facilitate rotation from transverse and posterior positions but give increased difficulty in extraction, and the Piper forceps, designed solely for delivery of the aftercoming head. Other less significant variations include the substitution of solid for fenestrated blades, minor changes in the cephalic curve, the use of narrow or wide shanks, and alterations in length, shape, and corrugation of the handles.

From this brief survey it appears that from the first model of Chamberlen to the latest instrument of the twentieth century, all creative thinking in design has been halted at the crossroads of a scissors lock. The vast number of modifications already suggested, however, reflects a profound dissatisfaction with the limitations of each instrument so far devised. If, therefore, one forceps could be invented to solve all or most of the problems of delivery, a very real stride would be taken in the direction of safe obstetrics.

*Presented at a meeting of the Chicago Gynecological Society, Jan. 17, 1958.

New Features in the Parallel Forceps*

The one element essential to any theoretically "perfect" forceps is that it must fit all fetal heads, whatever their size, with almost complete accuracy. Hence its blades must approach and separate in exact parallelism. To meet this exacting condition, a cephalic curve was constructed based on the constant ratio between the biparietal and bimalar diameters over which the blades fit in correct application. This fundamental factor was incorporated into a new forceps.

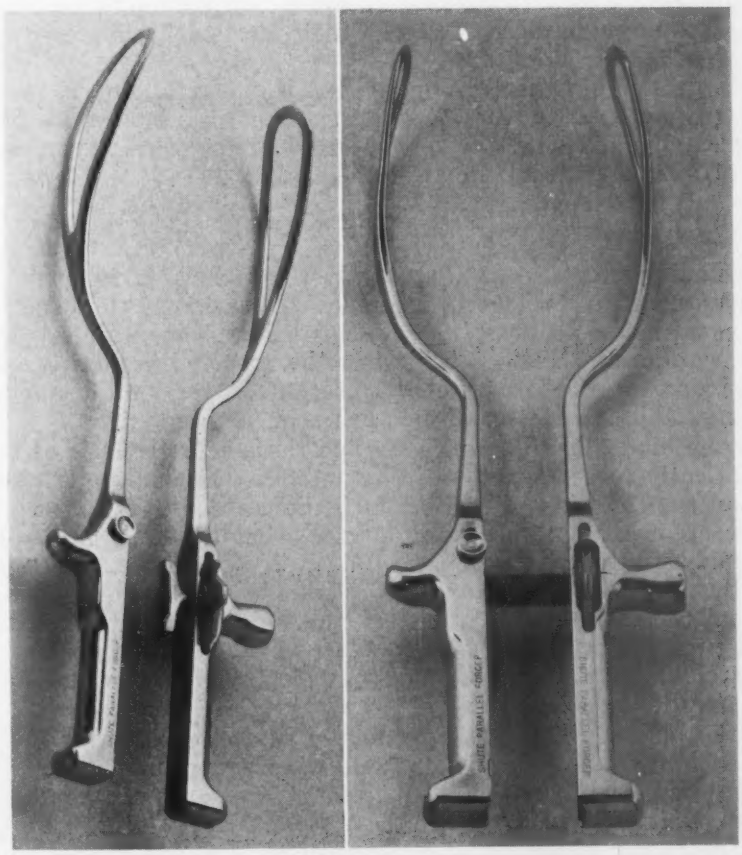


Fig. 1. Fig. 2.

Fig. 1.—Parallel forceps with blades separated.
Fig. 2.—Parallel forceps maximally opened.

It then became apparent that blades, fitting effectively over this area of the head, could be made much shorter. Thus their dangerous points could be eliminated and the pelvic curve retained with no more interference to straight, twisting rotation from transverse positions than in the Kielland forceps. The shanks devised for the new instrument were made slightly longer than those of the long DeLee forceps to render it equally adaptable to high midforceps and application to the aftercoming head. Finally, after much trial, a single locking device was evolved and perfected to match the complex, specialized

*The priority for the use of the principle of parallelism in obstetrical forceps has been established by photographs and descriptions of the first parallel forceps model, notarized in 1941. The parallel forceps was patented in the United States in 1956 and in Canada in 1958. Patents are pending in Great Britain, various European countries, and in Japan.

needs of a parallel forceps. Such a device had necessarily to be simple in construction, easy to lock without fumbling, completely rigid when locked, yet capable of instant disengagement at the will of the operator.

In detail, this lock consists of two moving parts imprisoned in the shank and horn of the left shaft of the forceps, and it may be described as follows:

1. A double-threaded screw works within a longitudinal bore at right angles to the axis of the forceps shaft which, when maximally retracted, is recessed within the traction horn of the handle. To prevent uncontrolled rotation the screw is keyed from below and so can move smoothly laterally without turning. Fused to its free end, i.e., projecting toward the opposing shank, is a rectangular piece of steel which forms a T shape with the axis of the screw.

2. A large nut or wheel is imprisoned in an axial slot in the left shank. This is deeply notched to allow easy, powerful rotation by the fingers. It is threaded and engaged with the screw, so that it controls all movement of the latter toward or away from the opposing shank.

Technique of Use

The technique for use of the parallel forceps is as follows: The blades (Fig. 1) are guided into place in cephalic application in the usual manner except that each, being accurately curved, can be inserted almost directly with much less wandering. Either blade can be inserted primarily, since in the parallel forceps the need for clumsy rotation of one handle about the other when the right blade is inserted first has been eliminated.

When the blades have been applied to the head, the heels of both handles are automatically forced together. The notched wheel in the left shank is now turned in an anticlockwise direction until the rectangular T piece of the screw enters a receptor slot at the junction of the right shank and upper handle. By continued rotation of the wheel the T piece is forced along an inclined entrance, thus separating the handles gradually until, when it sinks into the final vertical recess in the right shank, the forceps has attained exact parallelism. Then a pin, working in a vertical slot in the right shank, is drawn down to catch the upper arm of the T piece and fix it, thus locking the blades rigidly in parallelism.

Next, the blades, which are now merely in apposition with the head, must be tightened upon it to prevent slippage when traction is applied during delivery. They must not, however, be tightened more than the minimal amount necessary to resist the required traction, since otherwise they could seriously damage intracranial structures. By careful testing, the degree of tightening to achieve this end has been estimated. One complete turn of the wheel moves the screw through a distance of 4 mm. Hence each of the six notches of the wheel corresponds to a linear movement of 0.67 mm. of the screw. Therefore, to tighten the forceps on the head sufficiently to resist any ordinary traction, the wheel is reversed and turned in a clockwise direction through a distance of three notches. This approximates the blades at a distance of 2 mm. For very difficult extractions, the wheel may be turned through four or even five notches, thus tightening the blades upon the head by 2.8 to 3.5 mm. If these rules are properly observed, all but the slightest pressure marks upon the face should be avoided in even the most difficult deliveries.

Comment

The first parallel forceps was developed by the author in 1941, while resident in obstetrics at Cook County Hospital, Chicago. It was tested with his permission on Dr. Fitzgerald's service there, and successfully established the value of

this new principle. The present model of this instrument has been tested extensively by the author privately and on the obstetrical service at Cook County Hospital, upon all sizes of fetal heads presenting in all positions. From the results of these practical trials the advantages of this instrument over the usual scissors forceps appear to be as follows:

1. The blades move easily in complete parallelism, thus fitting every head accurately regardless of size (Fig. 2). Hence they do no violence to cranium, face, or skin.

2. While retaining their full pelvic curve, the blades are so much shorter than those of traditional scissors forceps that they can rotate a head from any position with a straight twisting motion, as easily as the Kielland forceps.

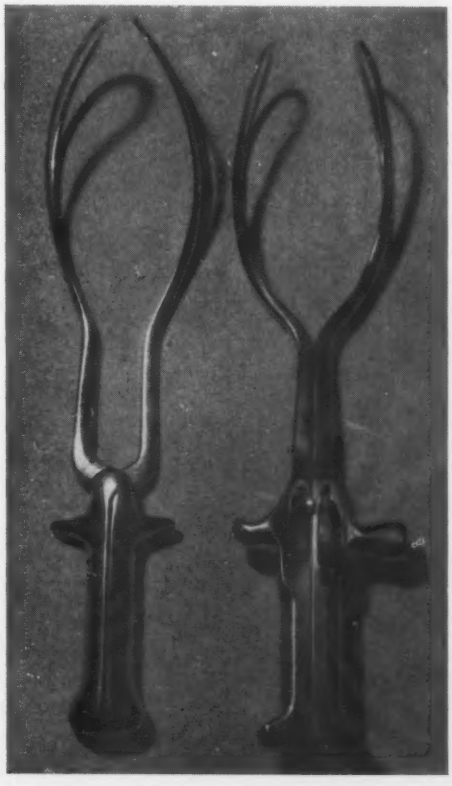


Fig. 3.—Parallel forceps and long DeLee forceps viewed from above showing the difference in the cephalic curve.

3. Since the cephalic curve is straighter (Fig. 3) and the blades narrower than those of scissors forceps, the parallel instrument can be applied more easily to any head in any position. Because of its simple locking mechanism, either blade can be applied first with equal facility. The length of the shank, moreover, makes the forceps as applicable to an aftercoming head as to a high midforceps delivery.

4. The mechanism of the lock is extremely simple—just two moving parts which can be articulated instantly, and as easily separated. The forceps can be cleaned and sterilized by all the standard methods.

5. The over-all shape of the new instrument varies but slightly from that which time and usage have maintained. Yet the technique of its use is very much simpler and more effective. Whereas the handles of the scissors forceps

are usually employed only as a means of directing the blades into cephalic position and during delivery are kept sedulously apart with a cautious thumb, the handles of the parallel forceps not only can, but should, be grasped firmly during extraction. No amount of compression of the handles after locking can alter the pressure on the head to the slightest degree.

In spite of tremendous advances in obstetrical instruction and hospital practice during the last several decades, it is inevitable that wide variations in individual techniques and skills must continue. Any instrument, therefore, which offers a simpler, unified solution to most of the problems of vaginal delivery should find a place in the obstetrical armamentarium. It is hoped, moreover, that in presenting a solution by one forceps of the difficulties of many, a significant contribution may be made toward the achievement of safety in parturition.

Summary

1. A brief survey of the historical development of the major principles in the obstetrical forceps has been given.

2. Basic criteria for the theoretically perfect forceps have been suggested.

3. A new type of obstetrical forceps is described which introduces for the first time the principle of parallel application of the blades, with a summary of its development and a description of its construction and the technique of usage.

4. The advantages of the parallel forceps over the usual scissors forceps are briefly discussed.

A NEW OBSTETRICAL INSTRUMENT

L. F. Zacharias, M.D., and Karl Ziesmann, M.D.,
Cincinnati, Ohio

(From Bethesda Hospital)

IN ORDER to obtain adequate vaginal exposure following delivery some method must be used to hold the cervix high in the vagina. For years it has been a common practice to use vaginal tampons, sponges, or, if available, traction on the fundus of the uterus by an assistant. The use of the vaginal tampon is dangerous and an actual hindrance if the episiotomy or laceration extends high into the vagina; it often hides active uterine bleeding; and it may inadvertently be left in the vagina.

Fig. 1.

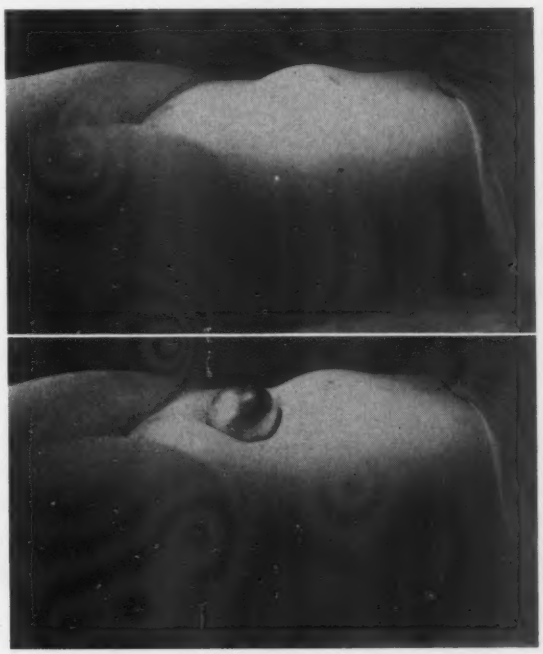


Fig. 2.

Fig. 1.—The fundus of the postpartum uterus is located at and below the level of the umbilicus.

Fig. 2.—Sphere in place; the fundus of the uterus is now located considerably higher in the abdomen.

An ideal method of getting vaginal exposure is by having an assistant retract the fundus of the uterus, thereby pulling the cervix upward out of the operative field. When the uterus is pulled up out of the pelvis there is less

congestion of the uterine and cervical vessels and, therefore, less bleeding. At the same time, the resultant traction on the vagina tends to align the lateral and medial walls of the episiotomy, making the repair easier. In many institutions, however, there is no assistant available, or in some instances it is necessary or more helpful to have an assistant engaged in other endeavors.

We should like to introduce an instrument that will retract the uterus and by so doing pull the cervix high in the vagina. For this purpose we have developed and used a very simple instrument—a steel sphere measuring 3 inches in diameter and weighing approximately 5 pounds.

Fig. 3.

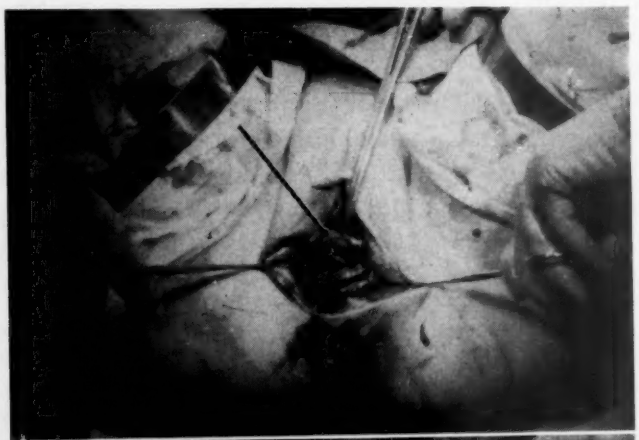


Fig. 4.

Fig. 3.—The postpartum cervix (arrow) partially covers and hides the episiotomy.

Fig. 4.—Sphere in place suprapubically *(8)*; the postpartum cervix is now retracted high in the vagina and the exposure of the vagina is excellent. The long pointer indicates the apex of the episiotomy.

Technique of Use

The fundus of the uterus is grasped through the abdominal wall and pulled upward. The sphere is then placed on the abdomen in the midline and just above the symphysis pubis. The sphere, therefore, lies in a hollow bounded by the lower segment of the uterus superiorly, the symphysis pubis

inferiorly, and the rectus muscles laterally (Figs. 1 and 2). The weight of the sphere is sufficient to keep this area depressed and, therefore, to hold the uterus up and the cervix in the upper portion of the vagina, and to align the episiotomy (Figs. 3 and 4).

The sphere may be used in two ways. It may be sterilized and placed on the sterile drapes by the doctor or may be left unsterile and placed under the drapes, directly on the abdomen, by the nurse or anesthesiologist.

In the short time that we have been using this instrument we have found that vaginal exposure is excellent. Any part of the vagina may be visualized without difficulty, with the aid of retractors placed in lateral vaginal locations.

Summary

A new instrument is presented which offers the advantages of:

1. Vaginal exposure without the use of tampons or need of an assistant.
2. Decreased immediate postpartum bleeding with a contracted uterus.
3. Alignment of the episiotomy.

We gratefully acknowledge the help of Mr. Karl Ziesmann, Sr., in the manufacture of the instrument.

DEPARTMENT OF CURRENT OPINION

Re-evaluation

UTOPIAN OBSTETRICS—IN RETROSPECT

R. A. Bartholomew, M.D., E. D. Colvin, M.D.,
William H. Grimes, Jr., M.D., J. S. Fish, M.D.,
William M. Lester, M.D., and William H. Galloway, M.D.,
Atlanta, Ga.

(From the Department of Obstetrics and Gynecology, Georgia Baptist Hospital)

AN ARTICLE entitled "Utopian Obstetrics" was published by one of us (R. A. B.) in 1942.[1] The title might better have been "Utopian Obstetrics—In Contemplation," inasmuch as the plan had not yet been put into effect because of the loss of two prospective key personnel to the Army at that time. The foundation, however, had already been laid by the informal association of the two senior members in the practice of obstetrics since 1930, each retaining his own clientele.

At the close of World War II, the absentees—a senior and junior member—were discharged from the service at nearly the same date and the time seemed opportune to establish a formal group practice since many patients had become accustomed to this type of care in the service hospitals, both here and abroad.

The manner in which a group is formed, the mechanism by which it grows to keep pace with the increasing clientele, and the regulations adopted to insure its stability and success will herewith be set down, based upon our own experience and that of other groups listed in the literature pertaining to group practice.

With growth of group practice, a nomenclature has been developed.[2, 3] A group is composed of not less than three members. One which represents several or more specialties is termed a Heterogeneous Group; one which is limited to a single specialty, a Homogeneous Group; one in which each member retains his own clientele is an Independent Group, either Homogeneous or Heterogeneous, whereas one in which the Group's schedule rather than the patient's preference determines who attends her is an Integrated Group, usually Homogeneous but possibly Heterogeneous, if large.

Obstetrics, Pediatrics, Anesthesiology, Psychiatry, Medicine, General Practice, and some of the subspecialties lend themselves well to integrated homogeneous group practice. Surgery, general or special, poses more problems perhaps, to both the patients and the group members, but the problems are not insurmountable, as is proved by the success of many large surgical clinics. Several or more integrated homogeneous groups representing various specialties are often component parts of an over-all heterogeneous group.

Motivations.[1, 3, 4, 5]—The first move in the direction of group practice is the informal association of two congenial, compatible, competent physicians in the same field of practice each of whom has an established practice and who desire to avail themselves of the advantages of: (1) reduction in overhead expenditures for rent, office personnel, supplies and equipment, (2) better availability of consultations or assistance, (3) substitution in case of illness, vacations, academic duties, or attendance on meetings, and (4) accustoming patients to the security afforded by occasional substitution or assistance when needed.

After some years of this type of practice, it becomes increasingly evident that an informal association, advantageous though it may be, does not furnish the complete answer. It does not provide for any release from the telephone, the constant pressure of responsibility day and night, the inadequate family life, and the recurring overload of practice occasioned by the alternate vacations of the associates.

The next logical step is a merging of the two practices into a formal partnership, in which neither physician is committed to render complete personal service to any particular patient but each seeks and requires the patient's complete acceptance of the partner who is on duty at the office or hospital, according to a prearranged schedule. Previous experience with the informal partnership will usually justify a belief that the assured presence of either partner at the time of the patient's admission to the hospital and throughout labor or on prenatal visits to the office will offer a compensating feeling of security and probability of acceptance of this type of care. It is fundamental that the acceptability of either partner should leave little or no preference in the minds of patients from the standpoint of competency, acceptability, and friendly, conscientious interest in the patient's welfare.

In our experience the two long-associated senior members decided it was feasible and preferable to omit the formal partnership step and proceed at once with the formation of a group of three members inasmuch as the prospective junior member was available and Board eligible. The necessary ingredients were at hand, i.e., an ample list of patients registered with the established senior

member, a potential list of patients likely to return to the ex-service senior member, ample office space in close proximity to the University Hospital, an available junior member, and certain motivations shared by all three, namely, (1) to enjoy a more normal family life, (2) to better preserve health, (3) to obtain more time for study, (4) to facilitate vacations and attendance on medical meetings, (5) to be protected against the disability occasioned by illness or accident, (6) to facilitate consultations and assistance, (7) to experience the stimulation that comes from a desire not to be found wanting, (8) to effect savings by sharing expenses, (9) to enjoy a more leisurely tempo of office work, thereby allowing more time for each patient, (10) to adhere better to an office schedule and avoid cancellations, (11) to assure complete coverage of office and hospital, days, nights, and weekends, and thereby the constant presence of a member of the group during labor.

Schedule of Duty.—The following schedule which pertains to shifts of duty at the hospital indicates the half or whole days each member spends in the office, the nights on and off duty, and the partial or whole weekends off duty.

TABLE I. SHIFTS OF DUTY AT THE HOSPITAL, REPEATED EACH THREE WEEKS FOR A GROUP OF THREE MEMBERS

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
First Week.—							
A.M.	A	C	B	A	C	B	C
P.M.	B	A	C	B	A	C	A
Night	B	A	C	B	A	C	A
Second Week.—							
A.M.	B	A	C	B	A	C	A
P.M.	C	B	A	C	B	A	B
Night	C	B	A	C	B	A	B
Third Week.—							
A.M.	C	B	A	C	B	A	B
P.M.	A	C	B	A	C	B	C
Night	A	C	B	A	C	B	C

When not on duty at the hospital, group member is at the office, except on weekends. For example, trace A for nights and weekends free of hospital duty.

Before activating group practice on the basis shown in Table I, it is necessary to acquaint patients with the plan by use of a form letter explaining the mutual benefits to be derived therefrom and requesting that those who do not wish to be attended under this plan inform the group and obtain a record of the care to date. If the patient desires, the group assists in obtaining services elsewhere.

It was gratifying, in our experience, to find that not more than a few patients withdrew. Subsequent comment indicated that the main appeal of group practice was the sense of security it afforded, particularly during labor. It was also significant that the question, "Who will check me or who will deliver me?" was noticeably absent after several months, indicating that those who registered thereafter understood that they looked to a group and not to a certain individual of their choice for total care.

As practice increases, it may be necessary to add a fourth member to the group. This is much facilitated if there are resident-training obstetric services in the city, which afford opportunity to contact desirable applicants. The group may possibly feel confident that a certain resident may be invited to join on a permanent basis at once. If there is any doubt, it is preferable to engage him on a salary basis for a year, with the understanding that at the end of this period his services will either terminate or be continued on a permanent basis. If there are no local resident services, a choice may be made through advertisements or medical personnel bureaus in which case a salary arrangement is preferable for a year of trial. While the decision to invite a new member should rest mainly with the group members, the wives should pass judgment also.

If the group numbers four, the following schedule may apply.

TABLE II. SHIFTS OF DUTY AT THE HOSPITAL REPEATED EACH FOUR WEEKS FOR A GROUP OF FOUR MEMBERS

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
First Week.—							
A.M.	A	D	C	B	A	D	A
P.M.	B	A	D	C	B	A	B
Night	C	B	A	D	C	A	B
Second Week.—							
A.M.	C	B	A	D	C	B	C
P.M.	D	C	B	A	D	C	D
Night	A	D	C	B	A	C	D
Third Week.—							
A.M.	B	C	D	A	B	C	B
P.M.	A	B	C	D	A	B	A
Night	D	A	B	C	D	B	A
Fourth Week.—							
A.M.	D	A	B	C	D	A	D
P.M.	C	D	A	B	C	D	C
Night	B	C	D	A	B	D	C

When not on duty at the hospital, group member is at the office, except on weekends. For example, trace A for nights and weekends free of hospital duty.

If it is felt desirable or necessary to increase the membership to five on account of age or partial disability of a member who could still work half days, the schedule for four members need not be changed. It would merely be necessary to work the half-day member at the office each morning and permit the one who has come off night duty to remain in the hospital and sleep until noon. By this arrangement, he would be sufficiently refreshed to share the afternoon work at the office and enjoy the evening as he wishes.

It is believed that those already in group practice, or possibly contemplating formation of a group, might desire a brief discussion of specific problems and suggestions as to how they may be solved. The following aspects of group practice in obstetrics are herewith briefly considered, in part based upon our own experience and beliefs.

Business Aspects of Group Practice[3-7]

Renting vs. Owning.—Medical Economics[10] upon investigating this question, concluded there was no decided preference. Certainly, in the early years of

growth of a group, renting is preferable, but does not preclude acquiring an advantageous building site which may increase in value during a period of waiting. It is most important for an obstetric group to work solely in one hospital and to rent office space or try to secure a building site in close proximity to the hospital. Assistance or consultation at the hospital may be necessary at any time and much time may thereby be saved. During the renting period, joint ownership may pertain to the furnishing of a reception room and the equipment of the business office. Otherwise, each individual member may be responsible for furnishing his own office and equipping his own examining room(s). Obstetrics requires minimal equipment; in many other specialties, joint ownership makes for greater economy.

Insurance Protection.—The group should be insured against accidents to patients, visitors, or employees on the premises. Malpractice insurance is mandatory upon the group as a whole (a joint expense) and upon each individual member (a personal expense). Bonding of the secretary for whatever amount needs to be protected over the accustomed period of audit, is a group expense; likewise, coverage for fire and theft.

Income and Expenses.—Receipts are given to patients for checks as well as cash, thereby simplifying audits. Periodically, the secretary requests from each member of the group a check made out to the group's expense account, the amount being determined by a like per cent of the gross income each member draws. These checks will total the amount the secretary is instructed to deposit. Group checks issued against the group expense account are signed by any two members of the group but not until the check is made out in full and the stub shows full details regarding the disbursement. Checks which have cleared and have been returned to the group are reattached to the corresponding stubs, likewise the receipted bill, which facilitates auditing. The items for which petty cash is disbursed are listed in a petty cash account book. Replenishment of petty cash funds is obtained by presenting a group check made out to and cashed by any member of the group; the stub shows it was drawn for petty cash. It should likewise appear in the petty cash receipts. Cash income is strictly for division among the members and is never used for any expense.

Entry and Division of Income.—Each day, checks and cash are entered in separate columns, checks being held for division on each weekend, cash being divided semiweekly. On the day of division, the totals for checks and cash are brought forward and the amount, determined by each member's per cent, is entered beneath his name and receipt acknowledged by each member initialing his amount. Division of checks and cash among the members can be totaled to a very small margin of differences. These small debits and credits are settled among members themselves. This simple method of bookkeeping has proved to be very satisfactory. The per cent of income assigned to each member determines his per cent of contribution to the expense account each time a deposit is requested. At the end of each month, the income in checks and cash is totaled. At the beginning of each year, any changes in per cent of income are entered under each member's name.

Policy Governing Division of Income.—The founder or founders of the group, who furnished the established practice(s) to build upon, are naturally entitled to the major shares of the income, when a third member is taken in to form a group. The per cent of income to be given to him depends greatly on the volume of practice at that time and the rate at which it is increasing. Incentive is encouraged much better by a percentage division of income than by a salary. The latter plan too often results in a voluntary separation from the group when a younger member feels he is sufficiently known to be able to withdraw and acquire some of the active or potential practice. Anticipating this possibility, some groups attempt to bind the younger member with legal restrictions, denying him the right to practice within a certain range of miles from the group's location over a certain period of time. The security features afforded by a group appear to offer sufficient protection against possible competition from a solo-minded member, without resort to legal barriers.

If the new member is chosen carefully and is offered the percentage incentive, our experience has been that he will remain loyal and satisfied as to his future. It has been our feeling that a new member will rapidly acquire the know-how of the older members within a period of five years and begin to contribute his share of the "pulling power" based on his own recognized qualifications. Nevertheless, seniority may still deserve some recognition in the form of a moderately higher per cent of the income for a few more years before equality is reached.

In general, by yearly adjustments, the younger members' percentages are increased and the older members' decreased until a level of equality is reached within five to ten years. It remains on this level until the acquisition of a new member or the attainment of partial retirement of one or more of the older members necessitates readjustment. It is assumed that a senior member may be released from delivery room and hospital duty at the age of 60, and further released to half days of work at the office from 65 on, as long as he is able and desires to perform this limited amount of office practice. With each limitation of work he voluntarily accepts a reduction in per cent of the gross income. Increase in volume of practice will often compensate to a considerable degree for the reductions. It is assumed that at this age of partial retirement he will have educated his children and accumulated sufficient reserve to retire if he so desires, or to continue at a much reduced per cent of income which would nevertheless represent the returns on a considerable total of savings. His contribution to the group in experience, counsel, and advisory capacity is still an asset to the group.

Are Certain Legal Stipulations Desirable or Required? [8, 9] Each member has some equity in the reception room furnishings and the equipment of the secretary's office—the older members probably more than the younger members. Theoretically, it is completely depreciated in ten years, but still represents some value considering the cost of replacement. This problem may be solved by stipulating a fair but arbitrary amount to be paid to the member at once on retirement or to his heir(s) at his death. In case of his death, permanent disability, or complete retirement, the member (or his estate) is

entitled to the per cent of the practice which had been booked and cared for up to the time of his separation from the group. To simplify bookkeeping during the extended period when care of these patients is being completed, it may be stipulated that the member or his estate will be given a lump sum which will fairly represent the anticipated return on these accounts and thereby settle the problem at once. This settlement may also be applied should a majority of the members of the group request a certain member to withdraw from the group. Half of the amount would seem fair should a member voluntarily withdraw from the group. A legal document may be drawn up and signed by the members to cover these stipulations.

Practical Arrangement of Duties.—Shifts of *office duty:* 9:30 A.M. to 1:00 P.M., 2:30 P.M. to 4:30 P.M. Shifts of *hospital duty:* 9:00 A.M. to 1:30 P.M., 2:00 P.M. to 6:30 P.M., 6:30 P.M. to 9:00 A.M. (one on duty in rotation on each shift). *Weekend duty:* 1:30 P.M. Saturday to 1:00 P.M. Sunday, 1:00 P.M. Sunday to 9:00 A.M. Monday (one on duty in rotation on each shift unless overworked).

Consultations.—These are easily supplied during office hours. If needed in the hospital, the member on duty requests members at the office to be put on the telephones; the problem is then stated, discussed, and treatment agreed upon. Assistance is furnished if needed. During the lunch hour, events of interest at the office, hospital, or homes are discussed.

Telephone Calls.—These are taken at the office during the day and at the hospital at night or over the weekend. Patients are specifically instructed in the prenatal folder of information not to call the residences, unless the condition is urgent and the member on duty at the hospital is temporarily unable to talk to the patient.

Records.—The history, examination, and prenatal record are taken on a printed tumbler form, which furnishes a carbon copy to be taken to the hospital at or shortly after delivery. A similar form supplied by the hospital furnishes a record of the labor, the baby at birth, a summary of the stay in the hospital, a record of the final examination at the sixth week, and an index listing the important data of the pregnancy, labor, puerperium, and the baby. The original of this record is taken to the office and a carbon copy of the same completes the hospital record. Each prenatal visit is initialed by the member who checks the patient, insuring that the visits are apportioned equally among the members of the group. Each member lists each patient in his personal memo book, which furnishes the essential data at all times. A prenatal folder of essential information and advice is given to each patient at her first visit. A blackboard in the staff room lists, in chronological order, the cesarean sections to be performed.

Decisions.—Any important issue, professional or otherwise, is decided by a majority vote of the members. This applies especially to any question which might have legal implications.

Dissemination of Information Among Group Members.—If urgent, a note is posted in the laboratory where it will be promptly seen, each member

checking off his initial, the last one placing the note in the patient's record. If not urgent, the note is initialed and passed from one office to another until all have seen it, the last one placing it in the patient's chart. Entries may also be made in the patient memo book carried by each member. Detailed information is given to each patient verbally at the first visit, because it is well known that some patients misplace or neglect to read the prenatal folder. This is an important factor in removing uncertainties, worries, and fears.

Financial Arrangements With Patients.—Variations in gross income of the husbands dictate variations in charge rather than inflexible fees. The wife's income is disregarded, since it is only temporary. This policy automatically takes care of fluctuations in time of prosperity or recession. Information about Blue Cross and Blue Shield or other coverage should be obtained. One half of the fee should be paid during pregnancy by regular monthly payments. Should payments exceed services rendered, as in the case of change of residence, an appropriate refund is given. Brackets of income from minimum to maximum, with corresponding graduations of increase in fee, enable the patient to set the corresponding fee which will cover the entire service excepting cesarean section, a complication requiring laparotomy, or circumcision of the baby. It is well to have a printed sheet explaining the care, cost, and the terms of payment.

Vacations.—Vacations are more enjoyable when taken without patients' protests and the overwork incident to departing and returning. Whatever the agreed period of vacation, it should not be exceeded except for good reason. Attendance on medical meetings, whether the member is on the program or not should not count against regular vacation allowance.

Academic Duties.—Voluntary teaching, whether didactic or in attendance on clinics or ward rounds, should be sought, if available, on account of the stimulation and incentive it affords. Moreover, the assignment can be fitted into the group's schedule with very little chance of interference with the office or the teaching schedules.

Value of Records and Index.—The uniformity and completeness of records greatly facilitate indexing which, with the volume of work performed, furnishes abundant clinical material for statistical investigations or research of a clinical kind. A promising lead or problem receives the combined attention of all members of the group. An index based upon good records cannot be maintained without conscientious and interested expenditure of time and effort. Rotation as to this duty should not impose much burden on any one member and the opportunity to make a final review of a case is most rewarding, inasmuch as it reveals the correlation of symptoms and signs, which of themselves would otherwise appear to be unexplained and isolated phenomena.

It is believed that the most rewarding, stimulating, and educational practice may be found in a group within a group, i.e., an integrated homogeneous group practicing as a component part of an integrated heterogeneous parent

group composed of a number of specialty groups. In such an organization, specialists of one kind contacting specialists of other kinds, formally or informally, widen their medical horizons by exchange of knowledge. Obtained in this manner, new knowledge seems to adhere to the recipient more firmly by the spoken word than by the written word, and practice becomes a daily round of postgraduate education.

The Future of Group Practice.—With care in selection of new members and adherence to principles and policies which have been found to be basically sound and acceptable, there is no reason why a group may not be self-perpetuating for many years, to the mutual advantage of the patients and group members. Although there are increasing evidences of encroachment of socialized medicine, we believe that group practice will continue to expand and be welcomed by a considerable segment of the population. The individual patient should be privileged to exercise free choice of the type of service preferred. To merit this preference groups must set for themselves high standards of efficiency and acceptability and dedicate themselves first and foremost to what is in the best interest of the patients.

References

1. Bartholomew, R. A.: Am. J. Obst. & Gynec. **44**: 553, 1942.
2. Rorem, C. R.: Canad. M. A. J. **70**: 462, 1954.
3. Porterfield, C., Marks, G., and Edgers, B.: California Med. **80**: 385, 1954.
4. Ollerenshaw, J. G.: Practitioner **170**: 619, 1953.
5. Goldstein, M. S.: J. Nat. M. A. **42**: 223, 1950.
6. Collings, J. S.: Lancet **2**: 31, 1953.
7. Goldstein, M. S.: J. A. M. A. **142**: 1049, 1950.
8. Stump, A.: J. Indiana M. A. **44**: 573, 1951.
9. Rubenstein, I. H.: Indust. Med. **20**: 513, 1951.
10. Medical Economics, Inc., Oradell, New Jersey: A Portfolio of Articles on Medical Groups and Partnerships.

Correspondence

Renal Hemodynamics in Normal Pregnancy

To the Editors:

We have read with interest the paper by Dr. de Alvarez in the May issue of this JOURNAL entitled "Renal Glomerulotubular Mechanisms During Normal Pregnancy," since the findings are in sharp contrast to the serial studies carried out in somewhat similar manner by us.[1] As pointed out by Dr. de Alvarez, the reported decline in filtration rate during pregnancy to the mean for nonpregnant women by the twentieth week of gestation is likewise in contrast to recent findings of Bucht in Sweden, and of Bonsnes and of Sohar and Levitt. It is a matter of considerable importance to establish the normal range of these functions for pregnancy in order to interpret findings in toxemic pregnancy. Our own results of 96 clearance studies are now in process of publication in full detail. The major findings may be summarized in Table I.

TABLE I. RENAL CLEARANCE OF INULIN AND OF PARA-AMINOHIPPURATE (PAH) IN NORMAL PREGNANCY

MEAN TIME (WEEKS)	NO. OF PATIENTS	CLEARANCE OF INULIN (ML./MIN.), MEAN ± S. D.*	CLEARANCE OF PAH (ML./MIN.), MEAN ± S. D.	FILTRATION FRACTION × 100 MEAN ± S. D.	ESTIMATED RENAL BLOOD FLOW (ML./MIN.), MEAN ± S. D.
Ante Partum.—					
15.2	12/11†	155 ± 22‡	770 ± 93‡	20.6 ± 3.5‡	1314 ± 200‡
25.1	11/11	152.3 ± 22‡	759 ± 77‡	20.1 ± 2.7‡	1217 ± 114‡
30.6	8/8	149.5 ± 20‡	699 ± 144	21.8 ± 3.0‡	1143 ± 259
33.8	7/7	162.8 ± 24‡	716 ± 171	23.7 ± 6.0‡	1119 ± 262
37.9	10/9	148.9 ± 21‡	588 ± 120	25.5 ± 4.0‡	943 ± 197
Post Partum.—					
46.7	8	97 ± 7.4	448 ± 100‡	21.2 ± 3.1‡	760 ± 183‡
53.2	6	96 ± 20	525 ± 70	18.7 ± 4.1	903 ± 161
65.0	6	103 ± 10.9	430 ± 50‡	24.1 ± 3.1§	760 ± 155‡
93.0	4	96.5 ± 13	580 ± 103	17.3 ± 2.7	856 ± 149
Nonpregnant normal women (average first and second clearance studies)	9	103.4 ± 9.75	599 ± 70	17.5 ± 1.6	1000 ± 139

*S. D. = standard deviation.
†The first number refers to the number of inulin clearances, the second of PAH clearances.
‡$p<0.01$.
§$p<0.02$.

Before the conflicting findings reported by Dr. de Alvarez can be accepted as definitive, certain points of technique not fully described in the published protocol of these studies should be established.

1. It was shown by Baldwin[2] in 1950 that if glucose is mixed with para-aminohippurate in the measurement of renal plasma flow, a complex is formed which is not cleared as readily as para-aminohippurate alone, thus giving an apparent depression of the PAH extraction ratio. Since solutions used in this study were prepared with 5 per cent dextrose in water, the lower values for renal plasma flow may be explained in part. Likewise, certain of the more common local anesthetics interfere with the analysis of PAH, and it would be helpful to know which were used.

2. The method of Schreiner, which was used for the determination of inulin in this study, does not include yeasting to eliminate glucose and free fructose. It is not clear

whether the brand of inulin used was clear of free fructose. Another possible source of error is that glucose in changing concentrations interferes with the analytical procedure. In recent studies from our laboratory,[3] we found that 100 mg. of glucose was equivalent to 1.4 mg. inulin. Thus, if no correction is made for dextrose given intravenously after blood is drawn for blank analyses, lower values for glomerular filtration will be obtained.

3. It has been demonstrated by Smith, de Wardener, Wolf, and others that pain or anxiety may depress renal function. It is important in a study of this sort to know what measures were used to minimize discomfort, and whether the subjects "secured and scheduled" through the ministrations of the U. S. Army may have reacted unfavorably to the serial studies.

4. If the filtration rate actually declines as profoundly in the latter half of pregnancy as indicated by Dr. de Alvarez's studies, one would expect consistent changes in the plasma concentration of those substances which are cleared predominantly by glomerular filtration. In our studies we found the range and mean of true plasma creatinine were sharply reduced and remained so during the entire pregnancy. We have similarly found that blood urea nitrogen drops to a mean of 8.7 ± a standard deviation of only 1.5 mg. per 100 ml. and remains in this range. One wonders in Dr. de Alvarez's study on what plasma concentrations of creatinine the clearance calculations were based, and also whether the modification of the method of Peters for the determination of creatinine included an adsorption procedure to isolate true creatinine from creatinine chromogens.

None of these factors, however, could entirely explain the reported progressive decline in renal function as pregnancy advances, but two additional considerations, may do so.

5. The possible effect of dextrose infusions in diminishing apparent inulin clearance described above might well increase, since the tolerance for glucose often is reduced as pregnancy advances and more hyperglycemia and glycosuria might be expected from the infusion of glucose.

6. Pritchard[4] clearly demonstrated that reabsorption of sodium and flow of urine are affected by supine posture. In our studies we could demonstrate no significant effect on filtration rate or plasma flow during short periods although certain individuals appeared to be so affected. We recently encountered a patient with moderate polyhydramnios whose filtration and plasma flow in the left lateral position were 149 and 738 ml. per minute, respectively, but in whom the values dropped to 104 and 564 ml. per minute while supine. The reported decline in renal function becomes more marked as pregnancy progresses. It is possible that the subjects were supine throughout the span of approximately 2 hours of the experiments and that the mechanical effect of the gravid uterus progressively depressed kidney function.

Until these points are clarified, we are hesitant to accept these results as definitive.

ETHAN A. H. SIMS, M.D.
Department of Medicine
University of Vermont College of Medicine

KERMIT E. KRANTZ, M.D.
Department of Obstetrics and Gynecology
University of Arkansas School of Medicine

JULY 3, 1958

References

1. Sims, E. A. H., and Krantz, K. E.: Clin. Res. Proc. 4: 142, 1956; and J. Clin. Invest. (In press.)
2. Baldwin, D. S., Schreiner, G. E., Breed, E. S., Wesson, L. G., Jr., and Maxwell, M. H.: J. Clin. Invest. 29: 614, 1950.
3. Welsh, G. W., III, and Sims, E. A. H.: Clin. Res. Proc. 6: 287, 1958.
4. Pritchard, J. A., Barnes, A. C., and Bright, R. H.: J. Clin. Invest. 34: 777, 1955.

Reply by Dr. de Alvarez

To the Editors:

I am most appreciative of the opportunity of receiving the comments of Drs. Sims and Krantz relating to our report on the renal hemodynamics during normal pregnancy.

While I have referred frequently to their results as presented in abstract form and as transmitted by others, it is indeed a real privilege to review for the first time their complete data as authoritatively presented by them in their letter and enclosure of Table I. Dr. Sims, writing in all good humor and equanimity, after reviewing our report, raises specific questions, many of which were asked by members of the Society of Gynecologic Investigation when a preliminary report of our results was given. Consequently we set out to answer these questions by conducting searching inquiries into our methodology and interpretation of the results obtained.

In the same benevolent and professionally inquisitive approach, we shall attempt to provide solutions to the dilemma which our results evoked, not only in the minds of most reviewers of our work, but of ourselves as well. We fully realize the unenviable position of presenting findings which represent a stand different from those presented in most previous reports.

In the first place, when Dr. Sims's data are graphically plotted and compared with the graphic representation of our own, the differences are only quantitative by a factor of approximately 30 c.c. per minute. The trend of his study and our own is similar throughout pregnancy.

We consider the experimental approach of the authors to be a valid one, and their forthcoming report as well as their enclosed data will most likely reflect painstaking precision in methodology. For uniformity in answering the questions raised by them, the answers will be numbered similarly to the questions in their letter.

1. We have reworked the procedures raised by Question 1 of their letter relative to the formation of a complex by the admixture of glucose and PAH in the determination of renal plasma flow. Duplicate samples, simultaneously obtained from the same patients, were analyzed, one with yeasting, the other without yeasting. No significant differences in the value of renal plasma flow were found, whether yeasted or not. In no instance was a local anesthetic utilized before, during, or even near the time of performing the renal function studies.

2. In the original paper presented by us, the method of Schreiner, without yeasting, was employed. We do know that the brand of insulin used by us was free of fructose. We have since run duplicate samples on patients studied by us, one including yeasting with values of glomerular filtration rate which are almost exactly the same as when yeasting was not employed. Where yeasting was carried out, it was applied to every sample of blood and of urine, and inulin clearance calculated just as in the duplicate samples where yeasting was not used.

Even though we consulted the authors' reference 3, we were unable to make a correction for intravenous glucose or to test their claim, inasmuch as the methodology for determining equivalance of glucose to inulin was omitted.

3. The influence of emotional factors on renal function has been demonstrated among patients studied by us and confirms the observations quoted. It was for this reason that the subjects were, as quoted by Sims, "secured and scheduled [sic]" through the ministrations of the U. S. Army. What was not brought out was the fact that the Army obstetrician who was arranging and scheduling these tests was a member of the academic faculty of our own Department, possessing the sympathy and understanding necessary for good patient care as well as the knowledge of the various factors influencing renal function. These patients represented an unusually cooperative, willing, relatively homogeneous cross-section of a group of young pregnant patients living in their own homes and being studied under no compulsion whatsoever. They were fully apprised of the investigational program and its objectives. On the other hand, the differences noted in Dr. Sims's data when compared with ours might well be open to the same criticisms raised by him. Is it not reasonable to assume that the emotional influences in a group of unwed mothers, cloistered in a Salvation Army home, pregnant for the first time, weighted with uncertainties of the future for themselves or their pregnancy, submitting as unwilling subjects to a research project, etc., might account for the values presented by their data?

4. As stated by Dr. Sims, we too noted that once the reduction of plasma creatinine occurred, it was sustained throughout pregnancy. In our paper, the data on creatinine

clearance were derived by performing a modification of Peters' method, but without adsorption procedure; even so, the difference in clearance in cubic centimeters per minute was not statistically significant. However, since receiving Dr. Sims's suggestion that the results would be significantly altered if this procedure were carried out, we did further modify the method. With the use of Lloyd's reagent in urine and serum to adsorb true creatinine, preliminary results indicate only a 4-10 per cent difference in results whether adsorption was used or not. Our creatinine determinations were performed on serum rather than plasma; our mean value during normal pregnancy was 0.79 mg. per 100 ml. There should be essentially no difference between serum and plasma creatinine except possibly a slight decrease if plasma were used; but even so one would doubt whether the difference would be much.

One could not agree more fully that any of the above factors could explain the progressive decline in renal function as pregnancy progresses. In investigations of this type, no single methodology is sacrosanct, but since in our study it was constant, carried out in the same surroundings, many clearances on the same patients, and by the same personnel, one wonders whether any other method would be attended by a different trend in the curve. Notwithstanding all this, our methodology and that of Dr. Sims cannot be very dissimilar, inasmuch as we both get exactly the same values for the normal nonpregnant patient.

5. All clearances in our group of patients were performed in a fasting state. No patient was glycosuric, since no patient was eligible for inclusion in our group of normal pregnant patients unless entirely normal. We have further tested patients after infusion of inulin in 5 per cent dextrose; none showed glycosuria. The question raised by Dr. Sims is valid, however, and deserving of investigation in the various types of advancing pregnancy. Patients in our clinic exhibiting reduced glucose tolerance at any time during pregnancy are considered prediabetic until proved otherwise by conventional means and by repeated postpregnancy follow-up.

One wonders how much dextrose clearance affects inulin clearance. One must also wonder whether it is justifiable to infer that the mass action of glucose is necessarily that of hyperinulinemia and inulinuria. Glycosuria represents a function of the tubular capacity for reabsorption of glucose which is not necessarily characteristic of inulinuria.

6. All our patients were, for the most part, supine during the renal function testing, but so is the patient with severe pre-eclampsia, eclampsia, and coma. This was intentional in order that we might evaluate the true differences between normal pregnancy and toxemic pregnancy. Studies currently under way in our laboratory are directed toward increasing urine flow, as suggested by Pritchard, in order to minimize the effect of position on the over-all clearance values which measure GFR and RPF. Our most current data reveal no significant difference.

As stated by Dr. Sims, no one factor can explain entirely the progressive decline in renal function with progressive pregnancy.

RUSSELL R. DE ALVAREZ, M.D.
Department of Obstetrics and Gynecology
University of Washington School of Medicine

NOV. 15, 1958

Further Comment on Hypnosis for Delivery

To the Editors:

Dr. Winkelstein, in his excellent article "Routine Hypnosis for Delivery," in the July, 1958, JOURNAL, correctly points out several shortcomings of hypnosis *as he used it* for alleviating the pain of childbirth. These are its unpredictability, and the additional time and constant supervision necessary.

In our early series (Kroger, W. S., and DeLee, S. T.: The Use of the Hypnoidal State as an Amnesic, Analgesic and Anesthetic Agent in Obstetrics, AM. J. OBST. & GYNEC. 46: 655, 1943), we, too, noted similar disadvantages. Since then we have been able to overcome these drawbacks, however, by employing hypnotic techniques which utilize the patients' own experiential background. For instance, the time involved in prelabor train-

ing and attendance during labor could have been drastically reduced, if he had employed autohypnosis and group hypnotherapy.

I personally feel that the extra time we devote to our patients, even if it involves somewhat longer attendance during labor, is valuable because there is no price too high for obtaining healthier babies, and for making childbirth a satisfying experience for all mothers. By training my patients in groups of twenty-five or more, in two one and one-half hour sessions per month, I actually save valuable office time, as all routine questions are answered during these sessions. Patients are instructed to ask all questions referable to pregnancy and delivery, except those of a personal nature, in the classes. They are, also, more readily hypnotized, because of the "emotional contagion" that occurs in the group. Understanding of hypnotic phenomena leads to increased motivation as the result of healthier identification with those who are successful in achieving hypnosis.

Furthermore, in the group setting, the inherent competitiveness of the female is mobilized. Overzealous individuals, however, who reject possible use of analgesia and anesthesia, are not taken for training. If such neurotic individuals fail to go through the entire delivery by pure hypnosis, they are apt, as Dr. Winkelstein points out, to become depressed. This is not an indictment of hypnosis per se, but rather a failure to recognize that such patients need the hypnosis for ego aggrandizement; they usually have to excel in some sphere in order to overcome deep-seated feelings of inadequacy. Therefore, a personality appraisal of all parturients, regardless of the type of anesthesia to be used, is indicated.

Another objection, namely, the unpredictability, can be dealt with if patients are informed, during the training sessions, that hypnoanesthesia is not an either/or method; that analgesia and anesthesia will be made available if requested; that they need not feel guilty if chemoanesthesia is required; nor have they "let me down." Such measures virtually eliminate the possibility of triggering a latent depression and other harmful sequelae.

I cannot agree with Dr. Winkelstein's statement, quoted from Forel, that "too many or too frequent sessions have a tendency to weaken the deeper effects of hypnosis." My experience, in thousands of inductions in several hundred patients, indicates that hypnosis has the opposite effects. For example, glove anesthesia and other phenomena of hypnosis often are not achieved until the sixth or seventh group training session. Drs. Winkelstein's and Forel's observations are undoubtedly true, if authoritarian or dominant techniques are utilized. These tend to mobilize critical attitudes and resistance. With permissive techniques, however, the hypnosis is actually woven into the fabric of the patient's own personality—patient-oriented hypnosis—and is more efficacious. Dependency on the operator is decreased. And, as the result of repetitive, positive, constructive conditioning achieved under hetero- or autohypnosis, the pain threshold is automatically raised in a much higher percentage of patients.

Dr. Winkelstein states that the mental attitudes, rapport, and confidence "in the procedure, as well as in the accoucheur, seemed to be as important factors as was the hypnosuggestion itself." This is not surprising, because hypnosis is not a "trance," altered state of mind, or unconsciousness. It is a mental set or attitude based on belief, faith, confidence, expectation—all catalyzed by the imagination. As such, there are no arbitrary delineations as light, medium, or deep hypnosis. In our present state of knowledge, no one knows where suggestibility ends and hypnotizability begins. Hypnosis, therefore, is to a degree present in all doctor-patient relationships, especially between obstetrician and parturient.

Since hypnosis depends upon a strong interpersonal relationship, it is obvious that, if an associate or resident is going to take over, he must establish a prior rapport with the patient, preferably during prelabor training sessions. Busy obstetricians, who find it physically impossible to be in constant attendance upon their patients, can train personnel to conduct the hypnosis during labor. The patients trained in autohypnosis, who can develop their own anesthesia, do not require constant supervision, observation, and fortification. These are seldom necessary in most cases.

Hypnoanesthesia *cannot and never will be* a substitute for chemoanesthesia. Therefore, patients must be informed that they do not sign a pledge against anesthesia, and

that it will be available if required. Thus, it naturally should not be recommended as a routine procedure for all parturient women, because of the varying degrees of susceptibility to it. Rather, hypnosis potentiates analgesia and anesthesia, and thus lessens fetal anoxia. Even when the routine use of hypnosis was evaluated, the author found its action satisfactory in 46.5 per cent of the series. How can a modality have shortcomings where almost half of the patients have less fear, pain, and apprehension? Furthermore, with the exception of those who developed amnesia (15.5 per cent), Dr. Winkelstein's patients actively participated in the birth process, and were also more cooperative. I no longer dissociate or utilize posthypnotic amnesia for pain relief, because most patients wish to participate emotionally in their labor. At best, less than 20 per cent can be delivered by such methods.

Hypnotic phenomena are a part of all human behavior. Because hypnosis is a multifaceted tool, its utility could be broadened, if it were used more often in conjunction with chemoanesthesia, and not for routine application. Also, group hypnosis training should have a more salutary effect by promoting a healthier acceptance among patients, especially if employed for its numerous advantages. Thus, the judicious use of hypnosis would be a boon to mother, child, and obstetrician.

WILLIAM S. KROGER, M.D.

104 SOUTH MICHIGAN BLVD.
CHICAGO 3, ILL.
OCT. 5, 1958

ITEM

Rules Governing the Award of "The Foundation Prize" of the American Association of Obstetricians and Gynecologists

1. The award which shall be known as "The Foundation Prize" shall consist of $500.00.

2. Eligible contestants shall include only (a) interns, residents, or graduate students in obstetrics and gynecology, and (b) persons with an M.D. degree, or a scientific degree approved by the Prize Award Committee, who are actively practicing or teaching obstetrics, gynecology, or engaged in research in these fields. No fellow of the Association shall be eligible to compete for this prize, and no candidates securing the award shall be eligible to compete again.

3. Manuscripts must be presented under a nom de plume, which shall in no way indicate the author's identity, to the President of the Foundation, together with a sealed envelope bearing the nom de plume and containing a card showing the name and address of the contestant.

4. Manuscripts must be limited to 5,000 words, and must be typewritten in double spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

5. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the official journal of the Association or, failing that, in a journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

6. Three copies of all manuscripts and illustrations entered in a given year must be in the hands of Jean Paul Pratt, M.D., Henry Ford Hospital, Detroit, Michigan, President of the Foundation, before April 1, 1959.

7. The award will be made at the Annual Meeting of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

8. The President of the American Association of Obstetricians and Gynecologists Foundation, Inc., shall annually appoint a Committee on Award, which, under its own regulations, shall determine the successful contestant and shall inform the Secretary of his name and address by May 15, 1959.

Inquiries for further details should be addressed to the Secretary, E. Stewart Taylor, M.D., University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, Colorado.